DIABETES IN NORWAY: COSTS, HEALTH-RELATED QUALITY OF LIFE AND COST-EFFECTIVENESS OF LIFESTYLE INTERVENTIONS

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1. ACKNOWLEDGEMENTS

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2. SUMMARY

Diabetes mellitus places a considerable burden on patients in terms of morbidity and mortality and on society in terms of costs. The number of individuals with diabetes is estimated at 160 000 in Norway, 170 mill globally. These numbers are expected to increase considerably in the future. The objective of this thesis was to increase knowledge about the costs and cost-effectiveness of diabetes interventions. The first sub-study explored the economic costs of diabetes in Norway, the second analyzed HRQoL in patients with diabetes and the third explored the cost-effectiveness of a lifestyle intervention.

Costs of diabetes

Using the prevalence approach, we included costs of in-patient hospital services, out-patient clinic visits, physician services, drugs, medical equipment, nutrition guidance, physiotherapy, acupuncture, foot therapy and indirect costs. Data were collected from national registers and responses to a survey of 584 individuals with diabetes.

The total estimated cost of diabetes in Norway in the year 2005 was NOK4.2 billion, which represents 2.4% of total national health care expenditure. The largest contributors to the costs were drugs, medical devices and hospital admissions. When hospital stays with diabetes as a secondary diagnosis were excluded, total costs were NOK2.49 billion. Pharmaceuticals accounted for NOK808 million (32%), disability pensions NOK408 million (16%), medical devices NOK340 million (14%) and hospital admissions NOK179 million (7%). Patient expenditures for acupuncture, physiotherapy and foot therapy were many times greater than those of nutritional guidance. Finally, the total costs of lost production from job absenteeism and premature mortality amounted to NOK596 million.

Health-related quality of life in diabetes

The aim of this study was to explore the impact of diabetes complications on health-related quality of life (HRQoL). We used the responses from a mail survey performed in Norway and asked about demographics, diabetes related complications and HRQoL using the EQ-5D descriptive system. The EQ-5D is a standardised instrument for use as a measure for health outcome. It is widely used, and by many governments a recommended instrument for measuring HRQoL. We explored the EQ-5D's ability to capture and represent typical complications related to diabetes.

Individuals without any self-reported diabetes complications had HRQoL in the range 0.85-0.90 on a scale from 0 (death) to 1.0 (prefect health). HRQoL was largely dependent on the presence of major diabetes related complications. Complications with the most severe impact were stroke, ischemic heart disease and neuropathy.

Cost-effectiveness of a diabetes intervention

We estimated costs and health outcomes of lifestyle interventions by means of the British UKPDS Outcomes Model. Data on the impact of diet and exercise on diabetes risk factors (HbA1c, blood-pressure, cholesterol, and body weight) were taken from a Norwegian trial on individuals with poorly controlled type 2 diabetes. Cost and HRQoL data were taken from paper I and II.

With immediate switch to insulin the estimated discounted life expectancy was 9.44 years (7.67 Quality Adjusted Life Expectancy (QALE)), while it was 9.48 (7.71 QALE), 9.53 (7.75 QALE) and 9.64 years (7.86 QALE) for two years, five years and lifelong lifestyle intervention. The discounted lifetime total costs including indirect costs of the four programmes were NOK283,637, NOK512,540, NOK799,245 and NOK1,417,004,

respectively. Compared with immediate switch to insulin, the costs per additional life-year were NOK6,053,073, NOK6,209,362 and NOK5,832,427 for two-year, five-year and lifelong lifestyle intervention, respectively. When the cost of time related to travel and participation in the diet and exercise sessions were disregarded, the costs per incremental QALY for the respective treatment courses were NOK40,656, NOK55,277 and NOK33,649. The results indicate that lifestyle interventions are not cost-effective unless society disregards indirect costs.

3. ABBREVIATIONS

CEA	Cost-effectiveness analysis
CHF	Congestive Heart Failure
CMA	Cost-minimization analysis
CUA	Cost-utility analysis
HbA1c	Glycosylated hemoglobin
HRQoL	Health-related quality of life
IHD	Ischemic Heart Disease
MAU instrument	Multiple Attribute Utility instrument
MI	Myocardial Infarction
NDA	Norwegian Diabetes Association
NLWA	Norw. Labour and Welfare administration
NOK	Norwegian crowns (currency)
OBGLD	Oral blood glucose lowering drugs
QALE	Quality adjusted life expectancy
QALY	Quality adjusted life year
QoL	Quality of Life
SBP	Systolic blood pressure
SF- 6	Short-form 6
SF-36	Short-form 36
SG	Standard gamble
TTO	Time trade off
VAS	Visual analogue scale

4. LIST OF PAPERS

I. Solli O, Jensen T, Kristiansen IS, Diabetes: cost-of illness in Norway, BMC Endocrine Disorders 2010, 10:15

II. Solli O, Stavem K, Kristiansen IS, Health-related quality of life in diabetes: The associations of complications with EQ-5D scores, Health and Quality of Life Outcomes 2010, 8:18

III. Solli O, Birkeland K, Aas AM, Kristiansen IS, Cost-effectiveness of intensive lifestyle intervention in patients with poorly controlled type 2 diabetes. Manuscript submitted

5. BACKGROUND

5.1. Diabetes mellitus

Diabetes mellitus is a disease characterized by inadequate insulin release and in type 2 diabetes also insulin resistance, which lead to abnormally high plasma glucose levels. People with type 1 diabetes produce little or no insulin at all because the beta-cells in the pancreas have been destroyed by an autoimmune process. In early type 2 diabetes the pancreas continues to produce insulin, and insulin levels are often even higher than in non-diabetic individuals. However, the insulin response after a meal is delayed and inadequate leading to compensatory increased plasma insulin concentrations during postprandial hyperglycaemia. The pathogenesis of hyperglycaemia and the insulin production in the body are illustrated in figures 1 and 2.

Figure 1 Pathogenesis of hyperglycaemia

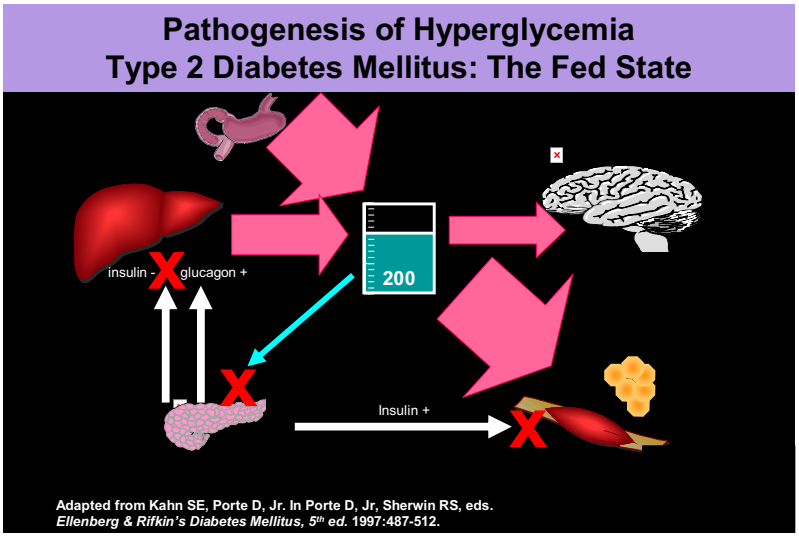
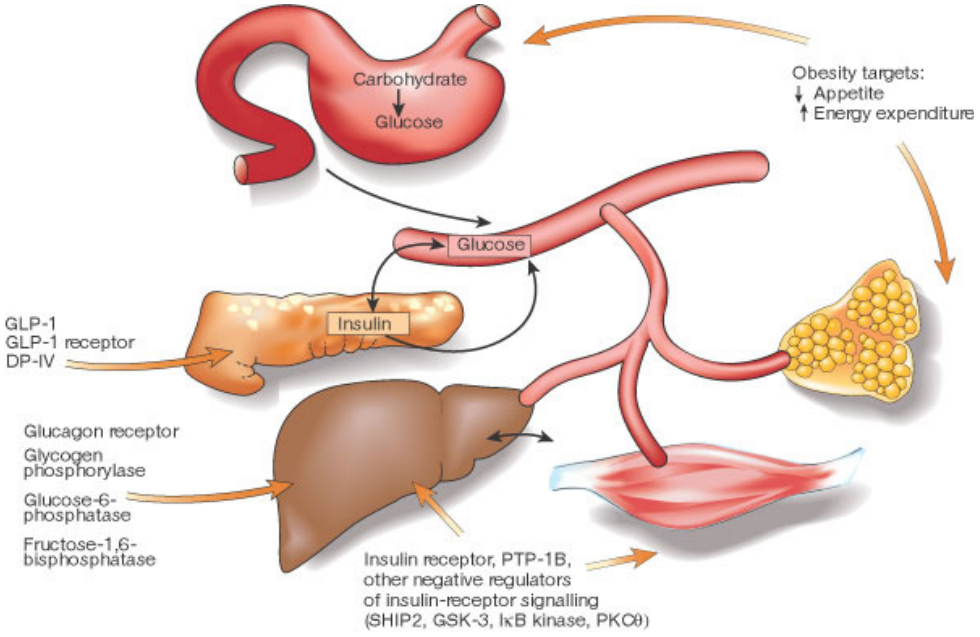


Figure 2 Simplistic model of the control of glucose metabolism



Type 2 diabetes is associated with obesity, and the increasing number of obese people is believed to increase the incidence and prevalence of diabetes. The age/sex specific incidence seems to be increasing in industrialised countries (1) although some research question this view (2). At least some of the increase in the prevalence of diabetes may be a result of increased attention and changed diagnostic criteria. There is little doubt, however, that the real prevalence of type 2 diabetes in Norway will increase as a result of demographic changes with an aging population over the next 30 years[1].

[1] http://www.ssb.no/samfunnsspeilet/utg/200401/01/

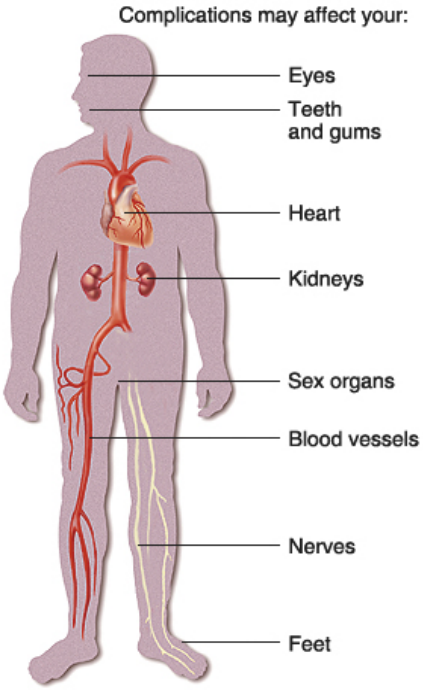
Diabetes complications (long and short term)

Untreated diabetes may lead to symptoms such as excessive urination (polyuria), infections, abnormal thirst and drowsiness. In the long run diabetes constitutes a risk of micro- and macrovascular complications. The first type encompasses retinopathy, nephropathy and neuropathy (including autonomic neuropathy). Macrovascular disease affects the larger arteries impairing blood supply to the heart, brain and lower extremities. A special complication is diabetic foot ulcers that usually result from a combination of neuropathy and reduced blood supply. Another macrovascular complication is the development of aortic aneurisms. In addition to diabetes-related complications, episodes of treatment-induced hypoglycaemia, fear of hypoglycaemia, change in lifestyle and fear of long term consequences may lead to reduced quality of life among individuals with diabetes.

The mixed pathophysiology entails a variety of clinical manifestations such as impaired vision, kidney failure, neuropathic pain, angina pectoris, myocardial infarction, stroke, ruptured aorta aneurisms and impaired circulation in the lower extremities (intermittent claudication, chronic leg and foot ulcers). Many of the complications require costly treatment such as renal replacement therapy and coronary interventions.

The clinical manifestations of diabetes lead to a loss of quality (3;4) and also quantity of life (5-9). Medical therapies such as renal replacement therapy, coronary intervention (PCI and CABG) lead to additional burdens for the patients. There is little doubt that diabetes leads to reduced health and further a significant loss in welfare to society. The reduced productivity following the increased morbidity and mortality adds to the burden of patients and society.

Figure 3 Overview of where diabetes-related complications may occur in the body



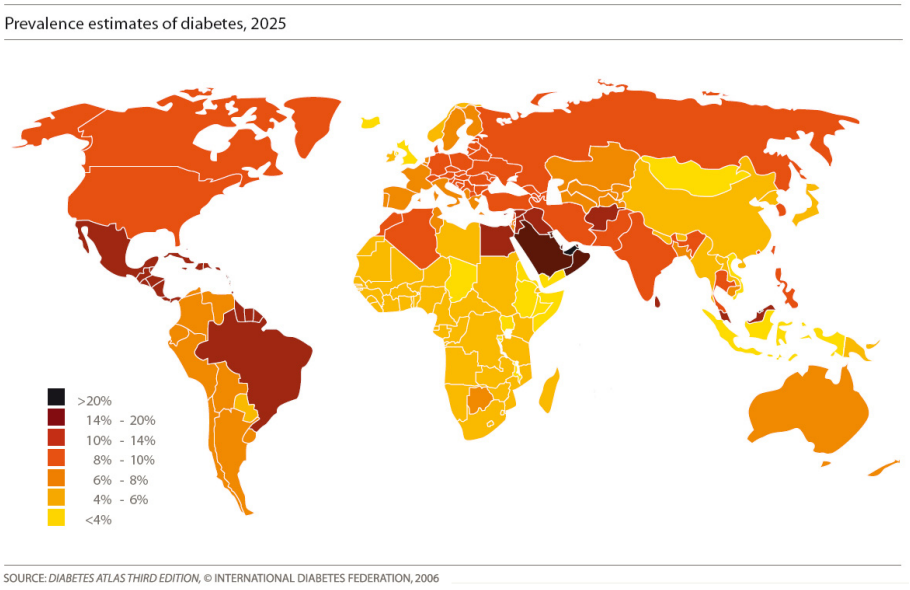
Source: healthline.com

Prevalence and incidence

The prevalence of type 2 diabetes is increasing in many countries (1) including Norway (10). The total number of persons with diabetes worldwide is projected to rise from about 170 million in 2000 to about 370 million in 2030 (1). The number of persons with diagnosed diabetes in Norway is estimated to be 90.000 - 120.000 of which most have type 2 diabetes (11). We have performed our own estimate based on the following. In Norway the number of patients with type 1 diabetes has been estimated at 25,000 (11). In 2005, 117,600 persons in Norway were treated with insulin or oral antidiabetics (information from Norwegian Prescription Database, searchable database). Based on this we assume that 92,600 of them have type 2 diabetes. In the Norwegian HUNT study (12) the proportion of

patients with type 2 diabetes that was not on antidiabetic pharmaceuticals, was 30%. This would imply that the total number of patients with type 2 diabetes is 132,300 (92,600/0.7) (11-14). Additionally, 30-50% of persons with type 2 diabetes are assumed to be undiagnosed. It has been estimated that about 3-4% of the population above the age of 30 have type 2 diabetes.

Figure 4 Projected global prevalence of diabetes in 2025

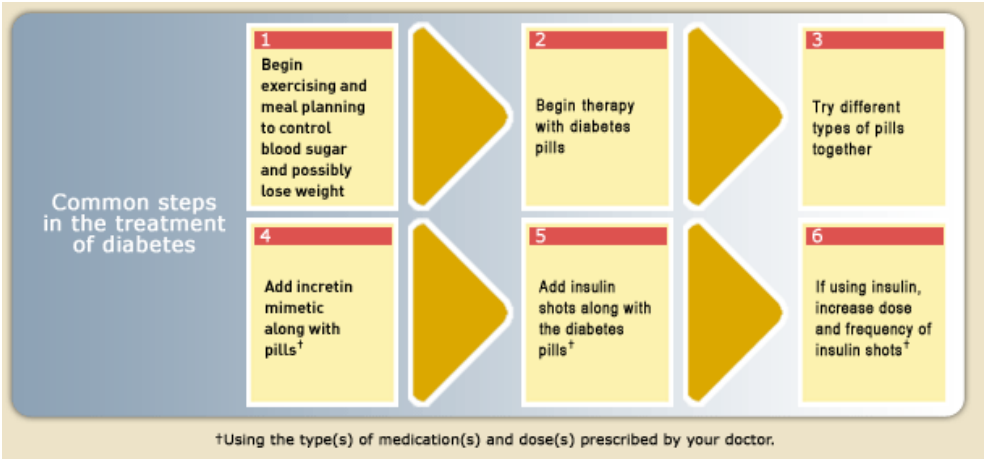


Treatment of diabetes

A range of interventions are available in the treatment of diabetes to prevent or postpone complications. In addition to blood glucose lowering therapies, various treatment aiming at preventing complications are essential. Most important are blood pressure lowering and lipid lowering agents. For type 1 diabetes the main medicines for regulating blood glucose levels are different types of insulin.

In type 2 diabetes patients the first step in the treatment is counselling on diet and physical exercise. The next step is to administer oral blood glucose lowering drugs (OBGLD), where metformin is considered as first-line therapy in Norway as well as in other Western countries. Subsequently, other OBGLDs with or without supplement of insulin may be applied (15).

Figure 5 Example of a diabetes-treatment algorithm



Effect of diabetes treatments

The effects of blood glucose controlling diabetes treatment are usually measured in so called intermediate terms such as glycosylated haemoglobin that reflects mean blood glucose levels during recent 2-3 months. From the literature we can find data on the consequences of having uncontrolled blood glucose levels over longer time periods. Such consequences may be short term complications (symptoms directly caused by hyper- or hypoglycaemic episodes) and long term complications (micro- and macrovascular) and loss of life years. Long term complications may lead to decreased quality of life. Methods of measuring quality of life, or in our context, health-related quality of life (more on this

below) have been developed and are widely used and adapted in quantifying effect of treatments.

5.2. Health Economics and diabetes

Limited health care resources and new and costly treatments have led to increasing demand among decision makers for documentation of "value for money" for new treatments. New tools for economic evaluation, and methods to analyze uncertainty, have been developed. When developing economic analyses of health interventions, analysts have to draw on data from numerous sources and synthesize them in a health economic evaluation. The two principal inputs in such analyses are costs and effect. For a complex disease such as diabetes the main goal of treatments is related to obtain stable and controlled levels of blood glucose and consequently quality of life. At the time when a new treatment reaches the market, there is usually little knowledge of long term costs and effect. This is particularly the case in diabetes because trials with clinical relevant outcomes ("hard outcomes") require long term follow-up. New interventions are therefore usually approved on the basis of surrogate endpoints such as HbA1c. This means that economic evaluation of diabetes interventions (drugs, lifestyle changes, etc) almost always have to be based on projections from surrogate endpoints to clinical relevant endpoints and subsequently to life years or QALYs.

6. AIMS AND OBJECTIVES

Against this background this thesis aims as generating knowledge about costs and health-related quality of life (HRQoL) related to diabetes and to perform a cost-effectiveness analysis of a specific intervention.

The aims of this thesis were threefold:

- To quantify the societal costs of diabetes in Norway and to provide researchers with a comprehensive set of unit costs for use in economic analyses.

- To investigate diabetes related determinants of HRQoL

- To estimate the costs and health consequences of a lifestyle intervention *versus* insulin in a group of poorly controlled type 2 diabetic patients.

7. THEORETICAL FOUNDATIONS

7.1. Cost-of-illness

Cost-of-illness analysis (COI) is a type of study that has been designed to quantify and value all economic consequences of a disease without taking into account the benefits of any treatment. In a COI analysis there is no measure of severity of disease or effects and side effects of treatments. Therefore, COI analysis in itself cannot guide priority setting, but may be useful in funding of health services and setting priorities for research. Furthermore repeated analyses undertaken at different points in time may be useful to monitor changes in resource use related to a disease.

There are two main approaches to COI analysis: the prevalence (16-20) and the incidence approach (21). The former approach accounts for all prevention, treatment and rehabilitation costs incurred during a given year. The prevalence approach has the advantage of relating to measures of total annual health care expenditure, and it may yield more accurate estimates because it is based, at least in principle, on observed costs rather than projected ones. With the incidence approach, all costs for new cases of the disease in a given year (the index year) are measured. Future treatment costs are accounted for by estimating the future costs for all patients who develop the disease in the index year, and the present value of the costs are added to the costs incurred in the index year. The advantage of the incidence approach lies in the fact that it provides projections of future costs that may be very different from current ones when incidence is increasing or declining. Such projections, however, may be uncertain (22).

7.2. Cost-effectiveness analysis (CEA)

In order to consider the cost-effectiveness of a health intervention it has to be compared with another intervention. The comparator may be no treatment, but it should be noted that even no treatment may entail resource use and health consequences.

The simplest form of cost-effectiveness analysis is the cost-minimization analysis (CMA). In this form of analysis the effects of the compared treatments are the same, or assumed to be the same, and only the costs are analysed and compared. Cost-effectiveness analysis implies comparing both costs and effect. When effects have a common denominator incremental cost-effectiveness is expressed with the incremental cost-effectiveness ratio (ICER) shown in figure 6.

Figure 6 The formula for calculating the incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{COSTS_{Treatment\_A*} - COST_{Treatment\_B*}}{EFFECT_{Treatment\_A} - EFFECT_{Treatment\_B}} = \frac{\Delta COSTS}{\Delta EFFECT}$$

*Treatment A is new treatment and treatment B is the comparator (examples: standard treatment, best option or cheapest option)

When the common denominator/effect is expressed in terms of quality-adjusted life years (QALY) the analysis is sometimes called cost-utility analysis (CUA). Figure 7, below illustrates when cost-effectiveness analysis or cost-utility analysis is required.

Figure 7 Choice of treatment and use of economic analysis according to costs and effect of treatment

		EFFECT OF TREATMENT		
		NEW BETTER	EQUAL	OLD BETTER
COST OF TREATMENT	NEW CHEAPER	*CHOOSE NEW* (NEW DOMINATING)	*CHOOSE NEW* **CMA**	**CEA/CUA**
	EQUAL	*CHOOSE NEW*	*INDIFFERENT*	*CHOOSE OLD*
	OLD CHEAPER	**CEA/CUA**	*CHOOSE OLD* **CMA**	*CHOOSE OLD* (OLD DOMINATING)

The ICER is an expression of the additional, incremental costs per extra unit of health of one treatment compared with another treatment or no treatment. The ICER value can be used by decision makers for priority setting. In principle, the production of health will be maximised by selecting treatments with increasing ICER's until the budget is exhausted. The ICER of the last treatment (the treatment with the highest cost per unit of outcome ratio) to be selected is called the threshold ICER. If the health care budget increases, treatments with higher ICER's may be selected, and vice versa, if the budget decreases, only the interventions with the highest value for money, the lowest ICER's can be selected. In practice, the ICER is compared with a threshold ICER. This threshold reflects the maximum cost per unit of outcome that the funder (government/insurance-company) is willing to pay for health improvements. If a treatment has an ICER below this threshold value, treatment is likely to be accepted by the funder and a treatment with a ratio over this threshold is likely to be refused. Treatments can be ranked from the lowest to the highest ICER in a so-called league table.

Prioritising based on ICER's implies that maximizing the production of health is the main or only goal of the health policy. However, in practice other considerations are taken

when prioritising, in particular considerations of equity, distribution of health and severity of disease.

When performing cost-utility analysis, the effect is measured in QALY's, described in section 6.4 below. This type of analysis has the welcome feature of incorporation both length of life and quality of life in one single measure and it allows decision makers to compare cost-effectiveness of treatments across different diagnoses and therapeutic areas.

7.3. Modelling

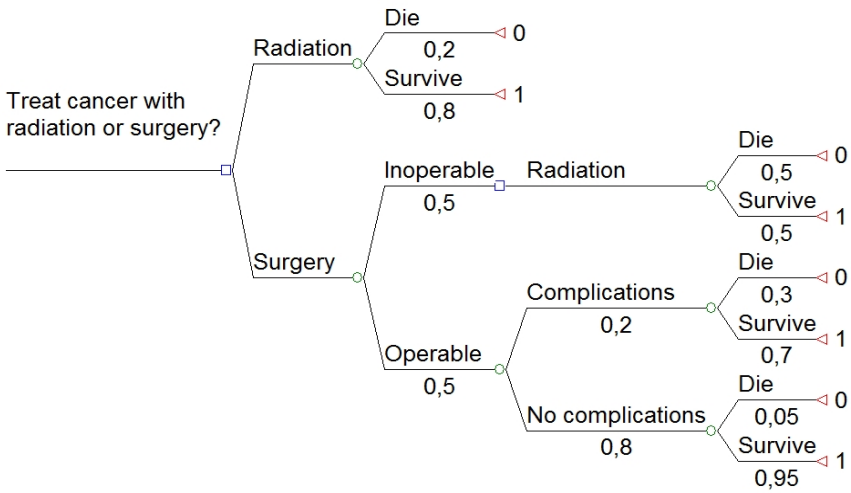
Clinical trials often have too short duration for adequate economic evaluation. Furthermore the output in clinical trials are often expressed in so called intermediate or surrogate endpoints such as HbA1c, mmHg, cholesterol level and others. In order to estimate cost-effectiveness in a relevant time perspective and using clinical relevant endpoint such as life years saved, quality of life, avoided fractures etc, modelling is needed in order to capture long term costs and outcomes. By extrapolating in time, place or patient groups, we aim to account for all costs in a relevant time perspective, adjusting costs and effect to present value (discounting).

Techniques used in health economic modelling:

1) Decision trees: This is a relatively simple form of decision analysis. The first branches of the tree usually represent strategies. The next branches illustrate different outcomes with probabilities attached. This may lead to further treatment options, also with probabilities attached. At the end of the final branches both costs and the "pay-off", or expected outcomes are denoted (this may be health status value or probability of survival. By "rolling back" the decision tree or calculating the expected value by multiplying probabilities throughout the tree and multiply this with both costs and the

pay-offs, one estimates the expected costs and expected value of each treatment strategy. These data enable an estimation of the ICER. This will so forth aid the decision maker when choosing treatment strategy.

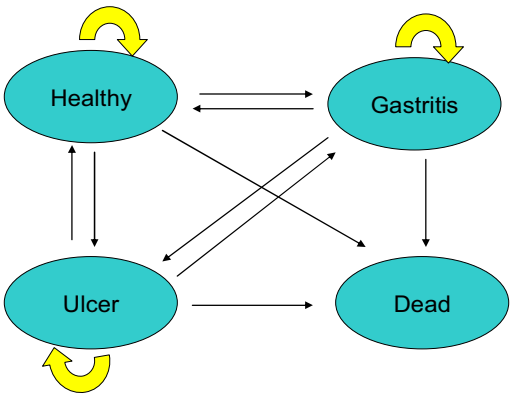
Figure 8 Decision tree (example for illustration)



2) Markov models: This is a more complicated type of decision analytic tool that accounts explicitly for time. A Markov model encompasses a set different health states and may include a health state for healthy and one for dead. The health state "dead" is often called the terminal or the absorbing state. In a Markov model the subjects in the model may move from "healthy" to "sick" and back to "healthy" again. In all health states the patient has certain probability of staying in the same state or moving to another. In the figure below, being in the health state "healthy" implies a probability of staying healthy, a probability of incurring gastritis, a probability of incurring an ulcer and finally a probability of dying. Individuals are at risk of moving to another state at fixed time intervals – the so called cycle length. The choice of cycle length depends on the

decision problem. A cycle length of one year is frequently used, but may be much shorter depending on the decision problem. Typically a move from healthy to "gastritis" would increase the probability of moving to "ulcer" or "dead". Being in a health state may involve a cost and a health state score. Often a Markov model starts out with a cohort of subjects and is run in cycles until all subjects are in the absorbing state, "dead". If a model is run multiple times with different probabilities associated to the transition between states (these probabilities may be derived from clinical trials) it is possible to analyse the difference in costs and health effects and calculate the associated ICER. A disadvantage of Markov models is that it is "history-less" (do not account for time and events in previous states). The impact of history on future costs and outcomes can be handled by creating new states that depend on previous events or states. This, however, increases the number of states in the model, sometimes to such an extent that the model may become difficult to handle. This issue may especially arise when applied in health economics due to the nature of health and disease, especially chronic disease, where disease history may greatly influence future health.

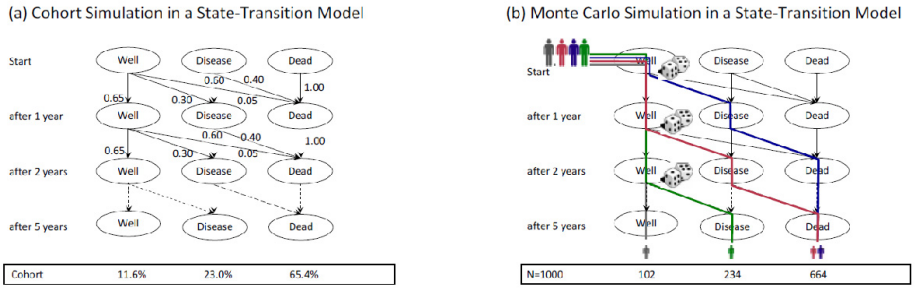
Figure 9 Markov model (example for illustration)



A Markov model is typically populated with a cohort of individuals and run in cycles until all individuals are in an absorbing health state (typically “dead”).

3) Microsimulation: Sometimes modelling time-varying patient characteristics is required in decision analyses. Microsimulation models are individual-based, simulating single individuals going through the model. These models utilize first-order Monte Carlo simulation to enable tracking of each simulated individuals history, which reduces the number of health states in the model. First-order Monte Carlo simulation may be described as running random trials and the draw of random numbers to decide a single path through the model. A disadvantage, that becomes less apparent with development within computer technology, is that these models require large computational resources and may take long time to run. An example of a microsimulation model is the UKPDS Outcomes Model, which was used in Paper III. The UKPDS Outcomes Model is an individual-level model developed to estimate long-term impact of health interventions for people with type 2 diabetes (23).

Figure 10 State-transition models (example for illustration)



Source: DRAFT – State-Transition Modelling: A Report of the ISPOR-SMDM Modelling Good Research Practices Task Force Working Group -Part 5, Siebert and colleagues. Available at www.ispor.org/workpaper/modeling_methods/DRAFT_Modeling-Task-Force_State-Transition-Modeling-Report.pdf

7.4. Cost-utility analysis and health-related quality of life (HRQoL)

The concept of quality of life (QoL) is a widely debated theme. What is QoL? Are we really measuring QoL or are we merely providing a measure for health status? Who should have a say when measuring quality of life? No general definition of QoL has been accepted or adapted. Despite the absence of a general definition of QoL there is a consensus that QoL is multidimensional, subjective and dynamic. Multidimensionality means that physical, psychological and social aspects are considered. Subjectivity means that a person should think about their own preferences and health status when measuring their own QoL. That QoL is dynamic means that it changes over time. Statements about quality of life are likely to be influenced by factors such as income, history and self interest of the individual. This raises the issue of the validity of the responses obtained.

In the context of economic evaluation we are primarily interested in HRQoL, this is a pure measure of health and functional status of the individual and excludes factors such as happiness and financial situation.

In order to obtain information on preferences of different health states and how a health state is valued, different techniques have been used. Preference-based methods such as the time trade-off method (TTO)(24;25), standard gamble (SG)(24) or the visual analogue scale (VAS) have been used in samples of individuals, aiming to derive utilities that can represent an entire population.

Time Trade-off

The time trade-off method is a technique where an individual is asked to imagine having a health problem lasting for a specific number of years. The question is then how many years in a reduced health state the individual is willing to sacrifice in order to obtain perfect

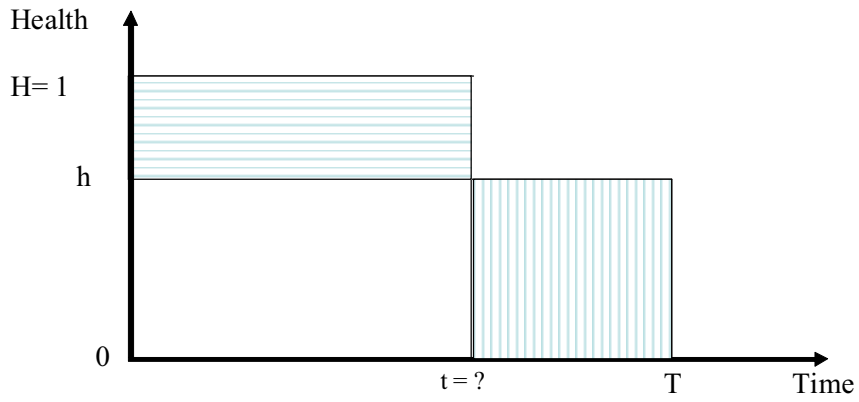
health. In other words, how much time is an individual willing to trade off in order to gain perfect health? This approach is illustrated by equation 1 and figure 11. The capital T is time in the state of reduced health, small h is the unknown value, on the 0 – 1 scale, of the reduced health state. Small h is the value we are searching for in this exercise. Capital H is the known value of perfect health, 1. Small t is the capital T minus the number of years the individual is willing to sacrifice to gain perfect health.

Equation 1 Value of a particular health state based on time-trade-off method (see figure below) (h=value of health state in question, H=value of perfect health, T=time in the health state in question, t=equivalent time in perfect health)

$$h \times T = H \times t, H = 1$$

$$h = \frac{t}{T}$$

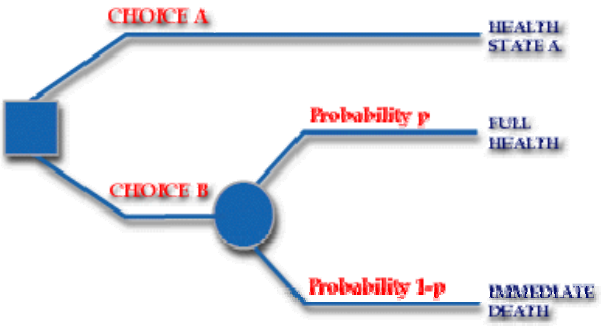
Figure 11 Graphic representation of the time-trade-off method (example for illustration)



Standard gamble

In this approach the individual is asked to imagine being in a state of reduced health (often described extensively) the rest of his/hers remaining life years. The next step is to imagine participating in a lottery, a gamble. The possible outcomes of this gamble are firstly the rest of the remaining life years in a state of perfect health and secondly immediate death (see figure below). The probabilities (p) in the gamble are varied until the individual is indifferent between being in the reduced health state and taking part in the lottery. If the individual is willing to take part in the lottery with a 0.9 chance of perfect health (and thus a 0.1 chance of immediate death), the value of the reduced health state is 0.9.

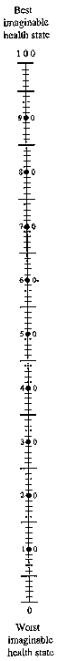
Figure 12 Graphic illustration of a standard gamble (example for illustration)



Rating scale (RS) or visual analogue scale (VAS)

This technique is the simplest form of eliciting preferences for health states. The exercise can be performed in different ways but basically the individual is asked to place different health states (often described in detail) on a scale ("thermometer") ranging from 0 to 100 (0 being death and 100 being perfect health) (see figure below). If one of the described health states is placed on 90 it means that this health state is considered to have the value of 0.9.

Figure 13 The rating scale (example for illustration)



Health-related quality of life instruments

The techniques described above are time consuming and complicated to administer. In practice, HRQoL instruments are most frequently used. There are three main approaches when describing and measuring HRQoL: Disease-specific instruments, generic instruments and utility instruments. Numerous disease-specific HRQoL measures exist for diabetes and score HRQoL on ordinal scales. Examples of such instruments are Diabetes Care Profile (DCP) (26), Audit of Diabetes-Dependent Quality of Life (ADDQoL) (27). These instruments are not useful as a single measure in cost-effectiveness analysis but may serve an important role of capturing diabetes specific features of treatment and effects.

Generic instruments such as the Short Form 36 (SF-36) (28) capture HRQoL and contains 36 items along 8 dimensions. Health profiles from SF-36 cannot be used directly

in economic evaluation, but John Brazier has developed methods to translate SF-36 profiles into utilities (30-33).

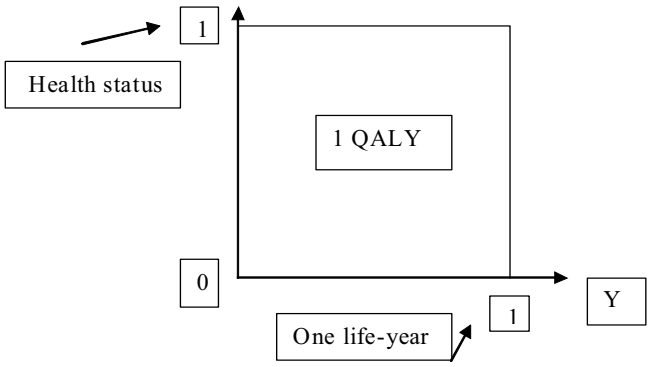
In multi-attribute-utility instruments (MAU), such as the EQ-5D (29), 15D (30), Health Utility index (HUI) (31;32) and SF-6D, which is a simplified version of SF-36, the respondents indicate levels of health problems on a number of dimensions of health. This can be done in a personal interview, telephone interview or by personally filling out a form. The questionnaire responses describe the health profile of the individual. These profiles capture different dimensions of health and can be translated into an index on a zero-one scale where zero denotes dead and one perfect health. In some instruments it is also possible to have values lower than zero. Such a value indicates a health state considered worse than death. Health status values are much debated (33-38). The translation of the scores from questionnaires into a single value representing an individual's health status index, are done by algorithms and value sets derived from population surveys (described above).

EQ-5D is a MAU instrument with five dimensions (MOBILITY, SELF-CARE, USUAL ACTIVITES, PAIN/DISCOMFOR and ANXIETY/DEPRESSION) and three levels on each dimension ("no-, some- and extreme problems"), and has previously been used in studies of diabetes (39). EQ-5D has been used extensively in economic evaluation. The EQ-5D is much debated because of its limited descriptive system and the possibility of health states worse than death (33-38). The EQ-5D is, despite the criticism, recommended for use in cost-effectiveness analyses by institutions such as the National Institute for Clinical Excellence (NICE) in the UK and the Health Care Insurance Board in the Netherlands. Therefore, researchers working with economic evaluation, health care workers and the pharmaceutical industry need easy access to utility data for different types of patients.

Quality Adjusted Life Years (QALYs)

When HRQoL weights (derived by TTO, SG, RS or MAU-instruments) are multiplied with duration (years, months, duration of effect, expected remaining life years) the product is named QALY (quality-adjusted life years) (se figure below).

Figure 14 Graphic illustration of one QALY (example for illustration)



QALYs can be calculated for different patient groups to compare for example effectiveness of treatment, enabling health improvements and life extensions to be captured in one single variable.

The concept of the QALY is based on a set of assumptions In a study by Weinstein and colleagues (40) the underlying assumptions of the conventional QALY approach are listed.

1. A resource-allocation decision must be made.

2. The outcomes of the alternatives can be specified in terms of health states, changes, and durations.

3. Resources are limited, and each alternative has resource implications (costs).

4. A major objective of the decision-maker is to maximize health of the population, subject to resource constraints.

5. Health is defined as value-weighted time (QALYs) over the relevant time horizon.

6. Value is measured in terms of preference (desirability).

7. Each individual is risk neutral with respect to longevity and has utility that is additive across time.

8. Value scores (preferences) measured across individuals can be aggregated and used for the group

9. QALYs can be aggregated across individuals; i.e., a QALY is a QALY regardless of who gains/lose it

7.5. Regression

Logistic regression

Multinomial logistic regression refers to at setting with more than two possible outcomes, for example “no problems”, “some problems” or “extreme problems”. Binary logistic regression, also called binominal, may be applied when there are only two outcomes, for example “no problems” or “some problems”. For ease of interpretation the outcomes are usually coded “0” (no problems) and “1” (some problems). The binary logistic regression is based on the assumption that the log of odds of the outcome is a linear function of a set of independent variables:

Equation 3 The model for logistic regression when facing binary outcomes (example for illustration)

$$\ln\left(\frac{p_m}{1-p_m}\right) = \beta_0 + \beta_1 x.$$

Note: $\frac{p_m}{1-p_m}$ gives the odds that a code of 1 will occur in the sample on any one opportunity. Logistic regression is a transformation of the dependant variable to the log odds ratio.

An example may be predicting whether a person reports having a mobility problem (EQ-5D mobility dimension) based on the presence of different co-morbidities.

Robust linear regression

The aim of regression analysis is to explore the relationship between one or more independent variables and a dependent variable. Ordinary least squares regression (OLS) is a commonly used method of regression and is based on the assumption that the dependent variable is a linear function of one or more independent variables. If the assumptions behind OLS are fulfilled OLS may be considered a preferred choice of regression model because it is relatively robust and because of computational ease. The main assumptions are: the model is linear in parameters, data are a random sample of the population, the errors are statistically independent from one another, the expected value of the errors is always zero, the independent variables are not too strongly correlated, the independent variables are measured precisely, the residuals have constant variance and that the error terms are normally distributed. When any of those assumptions are not fulfilled, OLS may yield biased coefficients. An assumption in a homoscedastic model is that the variance of the error term is constant for all values of x. However, for many real data sets, heteroscedasticity is the reality. Heteroscedasticity implies that the variance of the error terms is dependent upon x. The consequence is biased regression coefficients. Robust regression is a useful alternative to linear regression which means absolute error is minimized instead of mean squared as in linear regression. Robust regression usually means linear regression with robust (Huber-White) standard errors which means relaxing

the assumption of homoskedasticity. The effect of using White's correction is that in general the standard errors for the slope coefficients are increased relative to the usual OLS standard errors. This makes for more conservative hypothesis testing, so that more evidence against the null hypothesis would be needed before we would reject it.

8. ECONOMIC STUDIES OF DIABETES AND DIABETES INTERVENTIONS

8.1. Cost-of illness

In order to get an overview of the literature of interest we did a search (per 30.06.12) in PubMed with the search terms “Cost of Illness"[Mesh] AND diabetes”, limited to encompass reviews and systematic reviews. This search returned 240 articles. Studies of interest were studies of type 1 or type 2 diabetes, or both together. Both direct and indirect costs should be addressed. The language should be English, Swedish, Norwegian or Danish. After screening through the 240 titles 25 studies were kept. After screening the abstracts of the 25 studies four were kept.

The latest study in a series of COI-analyses performed by the American Diabetes Association was published in 2007 (17). The study turned up in our search even though it is not a review of existing literature. The objectives of the study was to quantify the economic burden of diabetes caused by increased health resource use and lost productivity, and to provide a detailed breakdown of the costs attributed to diabetes. The study used a prevalence-based approach that combined the demographics of the population in 2007 with diabetes prevalence rates and other epidemiological data, health care costs, and economic data into a Cost of Diabetes Model. Health resource use and associated medical costs were analyzed by age, sex, type of medical condition, and health resource category. Data sources included national surveys and claims databases, as well as a proprietary database that contained annual medical claims for 16.3 million people in 2006. The total costs of diabetes in 2007 were estimated to $174 billion. Excess medical expenditures and reduced national productivity accounted for $116 billion and $58 billion, respectively. Medical costs attributed to diabetes include $27 billion for care to directly treat diabetes, $58 billion to treat the portion of diabetes-related chronic complications that are attributed to diabetes,

and $31 billon in excess general medical costs. The largest components of medical expenditures attributed to diabetes are hospital inpatient care (50% of total cost), diabetes medication and supplies (12%), retail prescriptions to treat complications of diabetes (11%), and physician office visits (9%). The authors draw the conclusions that the actual national burden of diabetes is likely to exceed the $174 billion estimate. The reason stated is that the social intangible costs associated with pain and suffering, care provided by nonpaid caregivers, excess medical costs associated with undiagnosed diabetes, and diabetes-attributed costs for health care expenditures categories omitted from the study. Expenditure categories such as health care system administrative costs, over-the-counter medications, clinician training programs, and research and infrastructure development were also omitted from the analysis.

Several authors point to a 2004 review by Ettaro (41). The review examines the results of COI studies performed over the last three decades, identifies the strengths and limitations of the various methods utilized, and suggests future research that will help determine the economic burden of diabetes more accurately. The economic cost of diabetes is estimated to be as much as dollars US100 billion per year in the US alone (1997 values). The estimated cost has increased notably over time, primarily due to price inflation and the increasing prevalence of diabetes. Cost estimates are significantly influenced by differences in methodologies. This makes comparisons between COI studies difficult. The authors claim that in order to capture the costs associated with diabetes-related complications later studies have included costs related to diabetes as a secondary or tertiary diagnosis using the attributable risk methodology. Attempts at capturing these secondary costs are appropriate because of the long-term complications associated with diabetes. The authors suggest that future research efforts should focus on refining methods to estimate costs, improving the interpretation of study findings, and facilitating comparisons between studies.

Pagano and co-authors in 1999 presented a review (42) of studies on the costs of diabetes and its complications. In short, the authors find that many studies did not give technical details, so it was hard to understand the methods. Methodological choices varied widely between the studies. This is probably due to the lack of consensus on the methodology of COI studies. Pagano concludes that a general consensus on COI studies is still remote, making the value of any comparison of results questionable.

A study from 1992 by Leese (43) aim to presents a review of studies which have been carried out on the costs of diabetes and its complications. The study gives us some insight into what researchers found 20 years ago. The authors refers to a study that found that treatment of the disease and its complications takes up 4-5% of total health care expenditure in the U.K, costs are dominated by in-patient care for the complications arising from diabetes. The authors find it surprising that costs have not been more extensively researched for a chronic and potentially disabling disease with numerous complications such as diabetes. A large amount of data is available about the implications of diabetes in terms of incidence and prevalence. Little data on costs have been collected, particularly indirect and marginal costs. The authors claim that both insulin dependent and non-insulin dependent diabetic patients exhibit similar complications so that the cost of treatment may be comparable, but further studies are needed to establish this. Furthermore, apparently, few studies had included diabetes as a secondary diagnosis. The studies that were available at the time focused on direct costs. This is claimed to be so because they are the easiest to measure. Fewer studies included indirect costs, such as the effect of time lost from work, early retirement and premature death. Again, this is claimed to be a result of the difficulties in assigning monetary values to these factors. Finally the authors conclude that the most important contributors to the costs of diabetes are those of treating complications such as eye and limb disease, heart disease, neuropathy and nephropathy.

In a second search we looked specifically for diabetes related COI-research performed in the Nordic countries. We included studies of type 1 as well as type 2 diabetes, but excluded studies that did not encompass direct as well as indirect costs. The PubMed search resulted in the following:

- "Cost of Illness"[Mesh] AND diabetes AND Denmark. The search returned eleven studies of which none was considered relevant.
- "Cost of Illness"[Mesh] AND diabetes AND Finland. The search resulted in only six studies of which none was considered relevant.
- "Cost of Illness"[Mesh] AND diabetes AND Norway. This search returned six titles, but only one was relevant (Paper I in this thesis).
- Cost of Illness"[Mesh] AND diabetes AND Sweden. The PubMed search resulted in 36 studies. Among these, three were considered relevant to the questions discussed in this thesis.

The most recent Swedish study was from 2009 (44). The aim of the study was to estimate healthcare cost and productivity losses as a result of diabetes and diabetes-related chronic complications in Sweden in 1987 and 2005. Estimates on attributable relative risks and age-specific diabetes-prevalence rates were used to calculate the proportions of diabetes-related chronic complications that are attributable to diabetes. These attributable risks were applied to cost estimates for diabetes-related chronic complications based on data from population registers. The authors estimated total diabetes-related costs for Sweden in 1987 and 2005 to be EUR439m and EUR920m, respectively. Price estimates for 1987 were adjusted to a 2005 price level. The increase of 110% for the period 1987-2005 was estimated to stem from a 69% increase in the prevalence of diabetes (from 150,000 diabetes patients (1.8% of the population) in 1987 to 254,000 (2.8%) in 2005) and of an

increase in the estimated annual cost per person diagnosed with diabetes by 24%. Healthcare accounted for 45% of the estimated cost in 1987 and for 37% in 2005. The estimated diabetes-related healthcare costs accounted for approximately 1.0% of total health care cost in Sweden in 1987 and for 1.4% in 2005. Diabetes per se, excluding costs of diabetes-related chronic complications (also estimated in the study) accounted for 57% of the diabetes-related healthcare cost in 1987 and for 50% in 2005. Cardiovascular disease was the complication with the largest impact on diabetes-related healthcare costs, contributing to 33% of the healthcare cost, 27% of the productivity loss and 82% of deaths in 1987. The respective figures for 2005 were 34, 24 and 65%. The conclusion of the study is that the cost of diabetes is substantial and increasing even in a fairly low-prevalence country such as Sweden.

Another Swedish study (45) aimed to determine costs-of illness, including complications for adult diabetes mellitus. The source of study-participants was a previously conducted multicentre, cross-sectional study in which 1,861 patients were identified as having diabetes. A total of 1,677 of these agreed to participate in a cost-of illness study. Data were collected with interviews, systematic review of all available medical records. Co-morbidity was registered from all known medical records of health care. The average annual direct and indirect costs for an adult with diabetes were calculated to be Swedish crowns (SEK) 61,700 or 2.5 times higher than earlier estimates. The incremental cost per year of diabetes was 34,100 SEK. Direct health-care costs, defined as costs of out- and in-patient care accounted for 33% of the incremental costs. Costs for municipality services and home help from relatives (defined as services concerning food, alarm, cleaning and others) corresponded to 24%. Indirect costs were defined as lost productivity because of temporary impairment from sickness (sick-days) and permanent impairment (early retirement before 65 years)) and accounted for 43%. The authors raise the issue of

underestimation of diabetes costs if co-morbidity caused by diabetes is not accounted for. And finally they find that when related complications are included to identify the actual burden of disease to society, the cost COI is substantially higher than previously estimated.

Henriksson and co-workers aimed to estimate the total cost of diabetes mellitus in Sweden in 1994 and compare with former Swedish and American studies (19). The 1994 economic burden of diabetes mellitus in Sweden was estimated at 5,746 MSEK (1US$ = 7.50 SEK at the time of the study). The direct costs were estimated at 2,455 MSEK and constituted for about 43% of total cost. The indirect costs (production loss due to morbidity and premature mortality) were the dominant costs and amounted to 3,291 MSEK, or 57% of total cost. The comparisons with a previous Swedish study from 1978 indicated that the distribution of direct and indirect costs was about unchanged. The distribution of costs between management/control of the disease and complications was about the same for the two years. Four American studies showed a similar cost structure.

8.2. Quality of Life

For a search in PubMed we set a filter to languages English, Norwegian, Danish or Swedish. Searching PubMed with the search terms "Quality of Life"[Mesh] AND Diabetes" resulted in 3,617 studies. Furthermore, we restricted the search to include three instruments for measuring health related quality of life, the EQ-5D, SF-6D and the 15D. These instruments are of interest in the Norwegian setting as they are mentioned in the guidelines[2] for pharmacoeconomic analyses from the Norwegian Medicines Agency (NoMA). A search was performed for each of the three instruments. The criteria for including studies were: a aim of the study was to measure impact of diabetes related complications on health related quality of life among persons with type 1 or type 2 diabetes

[2] In Norwegian: www.legemiddelverket.no/upload/165659/11-08350-28%20Endelige%20reviderte%20retninglinjer%201%20%20mars%202012%20docx%20222688.pdf

(pre-diabetes, metabolic syndrome were not included), and use of the EQ-5D, 15D or SF-6D instruments. The following searches were performed:

- "Quality of Life"[Mesh] AND Diabetes AND EQ-5D. The search resulted in 85 studies among which 79 did not meet the inclusion criteria.
- "Quality of Life"[Mesh] AND Diabetes AND SF-6D. The search returned 11 studies among which ten did not meet the inclusion criteria.
- "Quality of Life"[Mesh] AND diabetes AND 15D. The search resulted in nine studies among which six did not meet the inclusion criteria

Among the six papers related to HRQoL, diabetes and EQ-5D, four were about type 2 diabetes (3;46-48), one did not make a distinction between type 1 and 2 diabetes (49) and one compared both types (50) (Paper II of this thesis).

One recent study (47) aimed to estimate the disutility related to experiencing a diabetes-related complication. The EQ-5D was administered to 1,147 Canadians with type 2 diabetes. The authors controlled for age, gender and duration of diabetes. Changes in utility values were estimated by Ordinary Least Squares regression of EQ-5D scores onto binary indicators for the presence of an event. Mean utility value for all patients, patients without complications and patients with at least one complication was 0.75, 0.76 and 0.70, respectively. Age and male gender was associated with higher utility values. Amputation, myocardial infarction, stroke and kidney failure were all related to significant reductions in utility. The respective coefficients for the before-mentioned clinical events were: -0.0631, -0.0586, -0.0462 and -0.01018. Kidney failure has the greatest negative impact on patients' HRQoL of the clinical events covered in the study.

A study of 220 Japanese patients with type 2 diabetes (48), used a Japanese version of the EQ-5D value set. The authors adjusted for age and sex before statistical analyses.

There was no significant relationship between EQ-5D scores and the presence of complications (neuropathy, retinopathy, nephropathy and lower extremity lesions). However the mean EQ-5D score was lower in patients with at least one complication (0.85) than in those without complications (0.88), but not statistically significant. The authors suggest that EQ-5D, which they claim is less sensitive than disease specific scales, should be used together with a disease specific scale for clinical evaluation.

In a 2002 UK study by Clarke and co-workers (46), the authors used data from 3,667 type 2 diabetes patients in UKPDS. Utilizing a Tobit model, the authors found that myocardial infarction, blindness in one eye, ischemic heart disease, heart failure, stroke and amputation reduced the HRQoL by respectively: -0.055, -0.074, -0.090, -0.108, -0.164 and -0.280.

In a study across five European countries (3) the aim was to gain insight into the impact of type 2 diabetes from the perspective of the patient. A total of 4,189 individuals were subjected to the EQ-5D questionnaire. The average score was 0.69 which is lower than score of healthy population in the United Kingdom with the same age. The mean values were higher (0.76) in the absence of complications. The presence of micro- and macrovascular complications impacted HRQoL negatively with scores of respectively 0.69 for both. Having both complications reduced the quality of life score to 0.59. Independent predictors of reduced HRQoL were explored in a multivariate analysis. Predictors, in order of importance were gender, complications, treatment type, age, obesity and hyperglycaemia. The authors conclude that the implication for policy-makers is that preventing or reducing the complications of diabetes is the key to improving patient HRQoL.

The aim of a US study (49) was to examine and quantify the differences in HRQoL of diabetic patients with and without macrovascular comorbid conditions. The study did not

distinguish between type 1 and type 2 diabetes. After controlling for age, sex, race, ethnicity, education, income, employment status, health insurance, smoking status, diabetes severity, and comorbidities, a two-part model was used to identify the relationship between macrovascular comorbid conditions and the EQ-5D index. Controlling for differences in sociodemographics, smoking status, diabetes severity, and comorbidities, the authors found that patients with macrovascular comorbid conditions had significantly lower EQ-5D index value of -0.062, compared to diabetic patients without these complications. The authors claim that the results of the study will be valuable for future comparative effectiveness and cost-effectiveness analyses in diabetes.

The one study using (51) SF-6D was a Greek study which compared the sensitivity of EQ-5D, SF-6D and the 15D to the specific effect of diabetes complications. On two different locations in Greece, physicians interviewed patients during routine visits to a diabetological outpatient department. The 319 patients were interviewed with the EQ-5D, SF-6D and the 15D. Furthermore the patients were asked about socio-demograpic- and diabetes-related factors. Coronary heart disease and diabetic retinopathy were chosen for further analysis. Significant EQ-5D, SF-6D and 15D predictors were identified with OLS regression and subsequently controlled for with ANCOVA. The presence of coronary heart disease resulted in significant utility decrements for all instruments, while diabetic retinopathy only significantly decreased the 15D utilities. After controlling for a set of confounding variables 15D still discriminated between diabetes with and without coronary heart disease (seven dimensions) affected and diabetic retinopathy (five dimensions affected). The authors explain this finding with the richer descriptive system of the 15D. The authors suggest the findings may be evidence for preferring the 15D in economic evaluations of interventions for diabetes.

Among the three studies using 15D only, two included type 1 diabetes patients (52;53) and one study included type 2 diabetes patients (same as the last study regarding SF-6D, described above).

The aim of a Finnish study (52), which used the 15D instrument on 1,023 patients with type 1 diabetes, was to assess HRQoL and its association with diabetic complications in a sample of individuals with type 1 diabetes. The participants were from a large study named the Finnish Diabetic Nephropathy study. The mean 15D score was 0.899. No difference between men and women was observed. HRQoL decreased with increasing age among patients with and without diabetic complications. By means of a Tobit regression model, reduction in HRQoL was explained by macroalbuminuria, dialysis, renal transplant, poor glycemic control, aging and longer diabetes duration with utility decrements of -0.036, -0.082, -0.053, -0.006, -0.002 and -0.001, respectively. Nephropathy affected all but five dimensions of the individual dimensions of 15D. Retinopathy affected vision, mobility, eating and usual activities. The authors conclude that the 15D scores decreased with increasing age. Reduced HRQoL was observed in persons with nephropathy. This was not the case for retinopathy.

A second study from Finland (53), with type 1 diabetes subjects, aimed to measure the impact of symptoms of diabetes-related long-term complications on HRQoL. Individuals were collected at random from the drug reimbursement registry of the Social Insurance Institution in Finland. 592 were included in the study as they met the inclusion criteria. Collection of data was done by a postal questionnaire with questions regarding symptoms, diagnoses and treatments indicating time of appearance and presence of long-term complications such as retinopathy, nephropathy, neuropathy, macrovascular complications (problems in arterial circulation and coronary heart disease) and stroke. Data on HRQoL were collected with the 15D. In order to estimate the effects of symptoms of

complications on HRQoL and to separate these effects from effects of other health problems and aging, the authors constructed a Tobit model. A markedly decline in 15D scores was observed with increasing age, and when the prevalence of symptoms of long-term complications increased. The Tobit regression model showed that these symptoms have a significant negative influence on HRQoL. The authors conclude that the high prevalence of symptoms of long-term complications combined with their significant negative influence on HRQoL causes substantial losses in terms of quality of life and utility from both individual and societal perspectives. Furthermore they conclude with emphasizing the importance of secondary prevention (prevention of complications by better metabolic control).

With few exceptions, little has been done in Norway to study quality of life among individuals with diabetes (54;55). In order to get an overview of research on quality of life and diabetes a broad search in PubMed with the search string "quality of life AND diabetes AND Norway" (search per 06.05.12) was conducted. Criteria for inclusion were: either 15D, SF-6D or EQ-5D was the instrument used in the study, study of HRQoL of diabetes (type 1, type 2 or both types) was the aim of the study, and lastly that the study was performed in the Norwegian setting. This search returned 50 titles. The only study that met the criteria for inclusion was Paper II of this thesis. The rest of the studies were either: performed in other countries, not studying diabetes (for example a series of studies on HRQoL related to diabetic foot ulcers) or utilizing disease-specific tools for measuring HRQoL.

8.3. Cost-effectiveness – diabetes – lifestyle interventions

Searching PubMed with the search-terms "diabetes" and "cost-effectiveness" returned 1,070 references, while the number is down to 357 if "diabetes" is replaced by "type 2

diabetes" (search performed 06.05.12). In order to increase the relevance of the search to the scope of this thesis we searched PubMed with the search terms ""Cost-Benefit Analysis"[Mesh] AND diabetes AND lifestyle. Criteria for inclusion were that a lifestyle intervention was studied, a cost-effectiveness analysis was conducted, that it was related to prevention or progression of type 2 diabetes, and that a simulation model was utilized. Studies related to screening for diabetes were excluded. The search returned 114 articles, among which 96 were excluded after reading the title and further ten were excluded after reading the abstract. This left us with eight studies of interest.

A Swedish study (56) investigates the cost-effectiveness of the Stockholm Diabetes Prevention Program, a community-based program during 1995 to 2004 in three municipalities, aiming to promote healthy lifestyles to prevent type 2 diabetes. The program focused on the preventable risk factors for type 2 diabetes (physical inactivity, poor dietary habits, obesity, and tobacco use, by means of both individual lifestyle and community change). The program seems less fixed and strict, with a main strategy of community organization and participation to develop community relations, and to educate and implement activities with local organizations. Effectiveness was measured in terms of risk factor levels in a population group aged 36-56 years at baseline and 8-10 years later (2,149 men; 3,092 women). Program municipalities were compared with a control area. With a Markov model future diabetes and cardiovascular disease-related health effects and societal costs were estimated in a cost-utility analysis. The study reports conflicting results regarding the cost-effectiveness of the program. The author still claims, due to the results from two study groups, that community-based lifestyle-programs aiming to prevent prediabetes and diabetes might be cost-effective.

The aim of a Dutch study (57) was to investigate the potential long-term health and economic consequences of lifestyle interventions for diabetic patients. Using a Markov

model (the Chronic Diseases Model), with a lifelong time horizon, the authors explored the health benefits and cost-effectiveness for these interventions when implemented in the Dutch diabetic population. The average gain in QALYS per participant ranged from 0.01 to 0.14. The costs were deemed to be reasonable being equal to or less than €50,000 per QALY. A self-management education program and physical activity counselling achieved the best results with a high probability of being very cost-effective with cost per QALY being equal to or lower than €20,000. The authors conclude that implementation of lifestyle interventions is likely to give important health benefits at reasonable costs, but the evidence for long-term maintenance of health benefits is limited.

The Finnish Diabetes Prevention Study was a randomized intervention program that evaluated the effect of intensive lifestyle modification on the development of diabetes mellitus type 2 in patients with impaired glucose tolerance. A 2007 study (58) utilized data from this study to explore whether such interventions are good value for money. A simulation model was designed to address the economic consequences of the intervention applied in a Swedish setting. Data from the trial were used to assess the effect of intervention on the risk of diabetes and on risk factors for cardiovascular disease. Risk of cardiovascular disease and stroke was estimated with the means of results from the United Kingdom Prospective Diabetes Study. Cost data were taken from Swedish studies. With a healthcare payer perspective, the model found the program to be cost-saving. The estimated increase in life years was 0.18. Cost-effectiveness ratio was €2,363 per QALY gained. The authors conclude that the lifestyle intervention directed toward high-risk subjects would be cost-saving for the healthcare payer and highly cost-effective for society as a whole.

In a Canadian study of individuals with impaired glucose tolerance (59), the authors aimed to compare the health and economic outcomes of acarbose[3], an intensive lifestyle modification program, metformin or no intervention, all used to prevent progression to diabetes. A Markov model was developed with four main states: impaired glucose tolerance, diabetes, normal glucose tolerance and death. Results from the Diabetes Prevention Study (mentioned above) and the Diabetes Prevention Program (to be described below) were utilized. Both of these were studies related to diabetes and lifestyle modification. These studies were used to estimate the impact of each intervention on transition rates between states. The results indicate that the treatment cost-effective way to prevent diabetes and may generate cost savings. Treatment with medicines tended to be less costly. Intensive lifestyle modification, if maintained, led to the greatest health benefits at reasonable incremental costs.

The Diabetes Prevention Program (DPP) (60) was a 27-center randomized clinical trial to determine whether lifestyle intervention or pharmacological therapy (metformin) would prevent or delay the onset of diabetes in individuals with impaired glucose tolerance (IGT), that were at high risk of disease. The study comprised 3,234 participants who were randomized to one of three study-arms, with 1,079 randomized to lifestyle intervention. The DPP lifestyle intervention was based on empirical literature in nutrition, exercise, and behavioural weight control, especially as it applied to the prevention of type 2 diabetes in diverse ethnic groups. The lifestyle intervention proved to be successful with a 58% reduction in the incidence rate of diabetes. Several studies have utilized data from the DPP study. Some of these are described below.

A study from 2005 (61) aimed to estimate the lifetime cost-utility of the DPP interventions with the means of a Markov simulation model used to estimate progression of

[3] According to the Norwegian Prescription Database there were 701 users of acarbose (Glucobay) in Norway in 2011.

disease, costs, and quality of life. The lifestyle and metformin interventions compared with the placebo intervention were estimated to delay the development of type 2 diabetes by 11 and 3 years, reduce the absolute incidence of diabetes by 20% and 8% and improve survival with 0.5 and 0.2 years, respectively. The cost per QALY was approximately 1,100 USD for the lifestyle intervention and 31,300 USD for the metformin intervention, compared with the placebo intervention. The interventions were estimated to cost 8,800 USD and 29,900 USD per QALY, respectively with a societal perspective. The lifestyle intervention dominated the metformin intervention with both perspectives. The authors conclude that health policy should promote diabetes prevention in high-risk individuals.

Another DPP-based study (62) reach a similar conclusion but comments that the program used in the DPP study may be too expensive for health plans or a national program to implement.

A 2004 DPP- based study (63) aimed to explore whether implementing the active treatments used in the DPP would be cost-effective in Australia, France, Germany, Switzerland, and the United Kingdom. With probabilities from the DPP and published data, and country-specific direct costs a Markov model was employed. The overall finding is that the DPP interventions could lead to an increase in diabetes-free years of life, improvements in life expectancy, and either cost savings or minor increases in costs compared with standard lifestyle advice in a population with impaired glucose tolerance. The conclusion draw is that financial constraints should not prevent the implementation of diabetes prevention programs.

In a 2003 study (64) aimed to assess (within the DPP trial) the cost-effectiveness of the lifestyle and metformin interventions relative to the placebo intervention. Again, top-line of the findings in the study was that the lifestyle and metformin interventions were effective and were cost-effective from the perspective of a health system and society (over

three years). The authors conclude that both interventions are likely to be affordable in routine clinical practice, especially if implemented in a group format and with generic medication pricing.

No studies similar to the study conducted in Paper III of this thesis were identified. The studies described above are different from Paper III in a number of ways. None of the studies investigated lifestyle-intervention related to progression of established type 2 diabetes and the avoided or delayed administration of insulin. One of the studies above was lifestyle intervention applied at a community level promoting lifestyle changes in the general population. The rest of the studies were mainly investigating the progression from impaired glucose tolerance to diabetes, or earlier stages of diabetes. The differences described above may explain differing results from the findings in our Paper III.

In Norway cost-effectiveness analyses have been performed mostly by the pharmaceutical industry in relation to reimbursement applications for medicines[4]. In Norway these applications are considered confidential, but an evaluation report from the Norwegian Medicines Agency is made public, sometimes with sections blacked out for confidentiality reasons. However in many cases when cost-effectiveness analyses are performed in Norway, they are based on input and data from other countries. A search in PubMed with the search terms "Cost-Benefit Analysis"[Mesh] AND diabetes AND Norway" show that little research is done in Norway. The search returned only nine studies, of which none are relevant to the scope of this thesis. Data specific for Norway should be used in economic evaluation or to provide information on the transferability of data from other countries.

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[4] www.slv.no/upload/139120/refusjonsrapport_levemir_mars2010.pdf
www.slv.no/upload/126455/refusjonsrapport_januvia_sept09.pdf

9. RESEARCH QUESTIONS

Paper I

The aim of this study was to estimate the health care costs attributable to type 1 and type 2 diabetes in Norway in 2005.

Paper II

The aim of this study was to describe how diabetes complications influence the health-related quality of life of individuals with diabetes using the individual EQ-5D dimensions and the EQ-5D index.

Paper III

The aim of this study was to estimate the (quality adjusted) life year gains and lifetime costs of two-year, five-year and lifelong lifestyle intervention compared to immediate switch to insulin in patients with poorly controlled type 2 diabetes.

10. MATERIALS AND METHODS

In the Cost-of illness study we set out with a desire to report results for type 1 and type 2 diabetes separately. During the data collection it became apparent that many of the data sources did not separate between the two types of diabetes. We therefore reported results separately as much as possible, and aggregated when this was not possible. In the HRQoL-study we relied on the self-reported diabetes type collected from the questionnaire. In the cost-effectiveness study the clinical input data were on individuals with type 2 diabetes. Data on costs and HRQoL were assigned accordingly.

10.1. Cost-of illness study input data

In order to capture costs related to diabetes we collected data from a range of different institutions and databases. To fill in the gaps of information not readily available we conducted a survey in a group of individuals with diabetes. The table below show the sources of cost data we used in the COI analysis.

Table 1 Data-sources used in the Cost-of illness study

	Cost factor	**Source of data**
Direct costs	In hospital care	NPR*
	Out-patient care	NLWA**
	GP and emergency visits	NLWA
	Private practicing specialist services	NLWA
	Insulin and analogues (A10A***)	NorPD****
	Oral glucose lowering drugs (A10B***)	NorPD
	Cholesterol lowering drugs	SURVEY/NLWA
	Antihypertensive drugs	SURVEY/NLWA
	Medical devices	NLWA
	Nutritionist guidance	SURVEY
	Foot therapist	SURVEY
	Physiotherapy	SURVEY
	Acupuncture	SURVEY
Indirect costs	Sickness compensation	NLWA
	Permanent disability pension and time limited disability pension	NLWA
	Basic and/or supplemental benefits	NLWA

* Norwegian patient register ** The Norwegian Labour and Welfare Administration *** ATC code **** The Norwegian Prescription Database **** Survey of diabetes in Norway 2006

10.1.1. Survey of diabetes in Norway 2006

Data collection

For various other types of resource use where register data are not available, we obtained information through a self-administered questionnaire. We developed a comprehensive questionnaire (see appendix 1) in collaboration with patients and doctors with diabetes care experience. The questionnaire was designed for optical scanning and capturing of data. The questionnaire was piloted twice, first among a selection of health care professionals employed in government and the pharmaceutical industry and secondly among county leaders in the Norwegian Diabetes Association (NDA).

In order to recruit persons with diabetes to a survey the possibilities are limited. However persons with diabetes have a Norwegian organization, (NDA). Membership in voluntary and the objective of the NDA is to promote diabetes related issues and maintain the interests of persons with diabetes in Norway. A large proportion of persons with type 1 diabetes in Norway are members of the NDA while only a minority of those with type 2 diabetes (about 15,000) are members, and some members are individuals with an interest in diabetes. After excluding persons under the age of 18 and non-diabetes individuals (health care workers and others with an interest in diabetes) NDA drew a random sample of 1,000 members from the membership file of NDA (36,000 members in 2006).

The questionnaire was mailed to the sample patients in May 2007. The respondents were asked to state their use of the following types of health care services for the previous three months: physiotherapy, acupuncture, nutrition counselling and GP home visits for hypoglycaemia. They were also asked questions about duration of the diabetes, type of treatment and occurrence of diabetic related complications. Non-respondents were followed up twice. The last follow up was accompanied by a letter written by the NDA, encouraging the participants to respond to the survey. When the survey was ended, we sent

all responses to a company specializing in optical scanning and capture of data. We performed a manual check of the data file we received after the optical scanning. This revealed a large number of inaccuracies and we had to perform a manual check of all questionnaires and manually correct the data file.

The questionnaire was approved by Regional Committee for Ethical Research and Norwegian Social Science Data Services.

Responders and non responders

Of the total 1,000 individuals with diabetes, 19 were excluded because they had died (n=4), had unknown address (n=13) or declined to participate (n=2). In total 598 of the eligible patients (61%) returned the questionnaire, of which 521 were complete and could be used in further analysis. Among non-respondents, 51% were female (based on first name) compared with 47% among respondents.

Among the 521 respondents, 165 were of type 1 diabetes (53% females), and 356 had type 2 diabetes (44% females). Mean duration of diabetes was 22 and 10 years, body mass index was 25.8 and 28.9, for type 1 and type 2 diabetes, respectively. With few exceptions the type 1 group reports using insulin and the type 2 group reports oral antidiabetic medicines. In the type 1 diabetes group 33% stated that they used antihypertensives and 28% cholesterol lowering drugs. The respective figures in the type 2 groups were 63% and 59%. More details and further descriptive statistics about demographics, risk factors for complications, medication and complications are shown in table 1, Paper II.

The only information we could obtain on non-responders was gender. We registered and counted the first names of all non-responders and found there was little discrepancy.

10.1.2. Data from the Norwegian Patient Register

A broad range of diabetes diagnose-codes were requested from the Norwegian Patient Register (NPR). The aim was to explore the use of diabetes-related diagnose-codes. We obtained information on all hospital stays with the following ICD-10 codes as main or secondary diagnosis[5]: E10, E11, E23.2, H28.0, N08.3, O24, P70.0, P70.1, P70.2, R73.0 and Z13.1. The codes P70.0, P70.1 (both gestational diabetes), P73.0 (pre-diabetes) and Z13.1 (encounter for screening for diabetes mellitus) accounted for a small fraction of the dataset (as main diagnosis, 175, 0 and 5 observations, respectively). The impact of these admission codes was deemed to be very small and we kept them in the further analyses for the purpose of covering a broad range of diabetes related codes. For each stay we obtained anonymous data on the primary diagnosis, secondary diagnoses, age, gender, geographic location, length of stay and DRG-weight. In Norway, hospital services are provided by five Health regional health authorities, each with an independent board. Geographic variation was analysed according to these five regions.

10.1.3. Data from NLWA

Out-patient clinic visits

Using the same ICD-10 codes as for in-patient services, data on the costs of out-patient clinic visits were provided by The Norwegian Labour and Welfare Administration (NLWA). No data for 2005 were available so data for 2006 were used. The NLWA data encompasses government reimbursements to hospitals. We added the standard patient co-payment per visit (NOK260). According to the financing model for hospitals,

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[5] E10 (insulin dependent diabetes mellitus), E11 (non-insulin dependent diabetes mellitus), E23.2 (diabetes insipidus), H28.0 (diabetic cataract), N08.3 (glomerular disorders in diabetes mellitus), O24 (diabetes mellitus in pregnancy), P70.0 (syndrome of infant of mother with gestational diabetes), P70.1 (syndrome of infant of a diabetic mother), P70.2 (neonatal diabetes mellitus), R73.0 (abnormal glucose tolerance test) and Z13.1 (special screening examination for diabetes mellitus).

reimbursements and co-payments encompass 40% of the estimated out-patient clinic costs. The sum was therefore adjusted upwards by a factor of 2.5.

Physician services

Data on the use of general practitioner (GP) services and private specialists were obtained from NLWA. Claim forms, 90% of which are delivered electronically to NLWA, are provided with ICPC codes. We obtained data on all visits with ICPC codes T89 (insulin dependent) and T90 (non-insulin dependent) diabetes. For each patient contact, we obtained data on diagnosis, type of contact, reimbursement and patient co-payment.

Medical equipment

The NLWA keeps account of reimbursement for diabetes self-tests and insulin injection equipment (injection catheters, insulin pens and needles, syringes, lancets for blood sampling). To avoid double counting, the costs of insulin pumps were excluded. Insulin pumps are administered in hospitals and costs are captured in the DRG costing system.

Indirect costs

Sickness compensation, permanent disability pension, time limited disability pension, and basic and/or supplemental benefits, are funded by the NLWA. We obtained data on all payments in 2005 for the ICD-10 diagnoses: E10, E11, E23.2, H28.0, H36.0, N08.3, O24, P70.0, P70.1, P70.2, R73.0 and Z13.1. A search was performed with all equivalent ICD-9 codes as well. Furthermore, the following ICPC codes were included[6]: T89, T90, W85 and F83.

[6] T89 (insulin dependent diabetes mellitus), T90 (non insulin dependent diabetes mellitus), W85 (diabetes during pregnancy) and F83 (retinopathy).

10.1.4. Data from Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) contains information on all prescriptions redeemed from pharmacies. We obtained data for 2005 on the following categories of ATC codes: A10A (insulin and analogues) and A10B (glucose lowering drugs). Additionally, we included the costs of patient reported use of antihypertensive drugs and cholesterol lowering drugs according to the findings in our survey. Data on the use of antihypertensive drugs and cholesterol lowering drugs were collected in the survey and a weighted average price per dose was calculated based on sales figures from 2005 collected from the NorPD.

10.1.5. Use of public registries in research

The cost-of illness analysis relies heavily on data from available data registers for the Norwegian health care system and The Norwegian Labour and Welfare Administration (NLWA). One major advantage of use of register data is that they encompass the total population and therefore in principle provides data on the total use of different types of health care. The use of registers should in principle reduce selection bias. Use of register data may have considerable limitations in terms of quality, however. Doctors and others who provide the data may be busy and less motivated to provide correct data. This may apply not least to diagnoses and procedures that influence cost estimates. Here, use of diagnosis impact funding of the hospitals, and hospitals may consider using inaccurate diagnosis to increase reimbursements. Some registers such as the Norwegian Prescription Database (NorPD) are likely to have very accurate data because they are based on redeemed prescriptions. Possible limitations of the NorPD are lacking registration of over-the-counter medicines, and incorrect or lacking personal identification numbers. The NLWA registers may be accurate in terms of actual costs, but the diagnoses may be inaccurate.

An alternative methodological approach would have been to collect high quality data for groups of patients and extrapolate to the total population. This however introduces uncertainty of the representativeness of the extrapolated sample.

10.2. Quality of life study inputs

Our HRQoL data stem from the survey described in section 10.1.1. The EQ-5D responses were translated into EQ-5D index utilities using the UK TTO tariff (25;65).

For descriptive statistics, we used means, proportions and standard deviations. Groups were compared using Fisher's exact test or the *t*-test. Determinants of EQ-5D dimension values were analysed by logistic regression. Because none of the respondents indicated level 3 ("extreme problem") for MOBILITY and SELF-CARE, we applied binary logistic regression to analyse these dimensions. For the dimensions USUAL ACTIVITIES, PAIN/DISCOMFORT and ANXIETY/DEPRESSION all three levels of severity were present and ordinal logistic regression could be used. The assumption of proportional odds was met when the two types of diabetes was analysed together, as assessed with a Brant test. Additional analysis, however, showed that the independent variables had differing impact on the dependant variable for the two types of diabetes. The proportional odds assumption was not met when type 1 and type 2 diabetes were analysed separately. Consequently, we performed separate binary logistic regressions for type 1 and type 2 diabetes and merged level 2 and 3 on the EQ-5D dimensions.

For the analysis of the EQ-5D index a number of regression models were considered. In order to obtain coefficients directly interpretable as decrease in HRQoL value we used a linear OLS regression model. The Breusch-Pagan test and plotting residuals versus fitted values showed that heteroskedasticity was present both for type 1 and type 2 diabetes. Therefore, we applied White's robust variance estimators.

The data were complete except for the covariates “Fear of hypoglycaemia” (13% missing), “Limitations at work” (23% missing) and “Limitations socially” (10% missing). Missing values were therefore imputed with regressions based on 15 independent variables (sex, age, weight, height and 11 diabetes-related complications). We used the impute function in STATA, which runs regressions by simple best-subset linear regression, looking at the pattern of missing values in the predictors.

We tested the covariates age and body mass index first as dummy variables divided in quartiles and second as continuous variables.

We chose covariates for the models based on input from health care professionals and knowledge of the disease. The aim was to choose covariates that could be associated with the dimension in question (example: amputation – MOBILITY and Neuropathy – PAIN/DISCOMFORT). In the binary regressions, we initially started with a full model and manually omitted variables one by one such that only statistically significant covariates were retained. The results from this approach can be seen in tables 6 and 7 (for the respective diabetes types) in the results section, and was chosen to identify the covariates with the greatest impact on each dimension. This approach was later, in a review process changed to retaining all covariates throughout the analysis, regardless of whether they were significant or not (see table 4 and 5, Paper II).

In the linear regression a full set of covariates was kept throughout the analysis in order to provide a full set of variables with both significant and non-significant impact on the covariates. The latter was done to provide a full set of results which may be used by other analysts in decision analytic modelling. All analyses were performed in STATA/SE 10.0 (Stata Corp, College Station, TX, USA).

10.3. Cost-effectiveness analysis of a lifestyle intervention versus insulin

10.3.1. Clinical data from the Aas et al. study

In the Aas study (66) thirty eight patients were randomized to one of the following strategies: 1) lifestyle intervention, 2) lifestyle intervention + insulin treatment and 3) insulin treatment alone. The lifestyle intervention consisted of 14 group meetings with dietary advice. Furthermore each participant had two individual sessions, focusing on advice and goal setting. The exercise programme consisted of group based exercise for one hour, twice a week. In addition, patients attended an individual consultation encouraging increased activity and energy expenditure. The study intervention lasted for one year. The baseline characteristics of all patients and in the randomized subgroups can be seen in figure 1, Paper III.

In total ten of the patients dropped out of the study (four due to illness and six due to non-compliance). Patients that did not complete the study did not differ in age or duration of diabetes, nor change in weight and HbA1c, during the run-in period. Dropout rates were similar in the three treatment groups.

The lifestyle intervention group experienced weight loss and a decrease in blood fat levels during the intervention year, while the two remaining groups gained weight. Patients were checked one year after the end of study with the results showing that the effect had disappeared during this time. The clinical data relevant for use in our modelling study can be seen in table 1, Paper III.

In order to populate the UKPDS Outcomes Model with the patients described in the Aas study more information was required. The authors were contacted and asked to provide us with data according to the list showed in the table below.

Table 2 Clinical data requirements for the UKPDS Outcomes Model

The items that need to be provided for each subject are*:	
ID	Subject identifier (optional)
Demographic characteristics	
Ethnicity	1=White-Caucasian, 2=Afro-Caribbean, 3=Asian-Indian
Gender	M=Male, F=Female
Age	Age in years at diagnosis of diabetes
Dur	Duration in years since diagnosis of diabetes
Weight	Weight in kg at diagnosis of diabetes [1.0 Kg = 2.2 pounds]
Height	Height in meter at diagnosis of diab [1.0 metre = 39 inches]
Risk factor values at diagnosis of type 2 diabetes	
Atrial Fib	Presence of atrial fibrillation (Y=Yes, N=No)
PVD	Presence of peripheral vascular disease (Y=Yes, N=No)
Smoking	Smoking status (0=Never, 1=Past, 2=Current)
Chol	Total cholesterol (mmol/l) [1.0 mmol/l = 38.6 mg/dl]
HDL	HDL cholesterol (mmol/l) [1.0 mmol/l = 38.6 mg/dl]
SysBP	Systolic blood pressure (mm Hg)
HbA1c	HbA1c (%)
Current risk factor values (leave blank if data not available)	
Smoking	Smoking status (0=Never, 1=Past, 2=Current)
Chol	Total cholesterol (mmol/l) [1.0 mmol/l = 38.6 mg/dl]
HDL	HDL cholesterol (mmol/l) [1.0 mmol/l = 38.6 mg/dl]
SysBP	Systolic blood pressure (mm Hg)
HbA1c	HbA1c (%)

* Full definitions of the input variables used are given in UKPDS 68.

We lacked data on characteristics of the patients at the time of diagnosis, however. In order to obtain these values we made the assumption that the patient had the same HbA1c values at diagnosis as at the start of the study. This was based on the assumption that at both these points in time patients have contact with the Health care system due to lacking blood sugar control.

10.3.2. The UKPDS Outcomes Model

Ideally we would have developed a Norwegian diabetes model, totally representative of the Norwegian diabetes population, with all epidemiological, cost and quality of life values collected and derived in Norway. Unfortunately, most of the necessary data, not least the epidemiological ones, are not available for Norway. Also, the development of such a model was beyond the time resources of this PhD project. We therefore chose to adopt a model developed elsewhere. A number of models have been developed and could potentially be

used (67-69). The choice of model was discussed with health economists with experience with diabetes modelling in other countries, and they recommended the UKPDS Outcomes Model. We therefore chose to use the UKPDS Outcomes Model because of its availability, because it is based on a large UK observational study and because it only requires standard software (EXCEL).

At the time the UKPDS Outcomes Model was developed a number of models were already available. However, the authors presenting the UKPDS Outcomes Model (23) found that there were major limitations to most of the models. For instance one of the models present at the time utilized data from a type 1 diabetes trial, and derived its cardiovascular risk estimates from the Framingham cohort study (70). This was a major weakness because the Framingham study only encompassed 337 patients with type 2 diabetes. This could mean that the basis for cardiovascular risk in the model could be inaccurate.

The United Kingdom Prospective Diabetes Study (UKPDS) (71) was a multi-centre, prospective, randomized, intervention trial of 5,100 newly-diagnosed patients with type 2 diabetes, the largest clinical research study on diabetes ever conducted at the time. The study aimed to determine whether improved blood glucose control could prevent complications and reduce the associated morbidity and mortality. The UKPDS did provide evidence that the serious complications related to type 2 diabetes can be significantly reduced by appropriate treatment. The UKPDS resulted in a range of publications, and is frequently cited. Utilizing data from the UKPDS study became a well validated data source of diabetes-specific data. A search for “UKPDS” in PubMed returns 456 papers.

The UKPDS Outcomes Model (23) is based on data from the above mentioned United Kingdom Prospective Study (UKPDS). The aim of the study presenting the UKPDS Outcomes Model was to develop a simulation model for type 2 diabetes that could

be used to estimate the likely occurrence of major diabetes-related complications over a lifetime. This could in turn be used to calculate health economic outcomes such as quality-adjusted life expectancy (QALE). The UKPDS Outcomes Model is a large integrated system of equations used to forecast major diabetes related complications. The simulations are based on a probabilistic discrete-time illness–death model. The cycle length is one year. When running the model the patients start with a given health state, for instance a certain set of parameter values and no complications. In any model cycle the patients may have one or more non-fatal complications and/or may die. The UKPDS Outcomes Model is based upon 14 risk equations (see appendix 5-7). All equations are survival functions derived from UKPDS. Seven of the equations are event functions, each describing the probability of experiencing a diabetes related event/complication (MI, IHD, CHF, renal failure, blindness, amputation and stroke). Three of the equations are mortality functions. One describes the probability of a diabetes related event being fatal, one the probability of death for a person with diabetes and the last one death from other causes. The four last equations are risk functions relating to how different clinical parameters influence the probability of death (HbA1c, SBP, HDL and smoking).

The UKPDS Outcomes Model enables estimation of confidence intervals for estimates of Life Expectancy, Quality Adjusted Life Expectancy and complication costs. The following is stated about this in the UKPDS Outcomes Model manual:

“The software contains full sets of model equation parameters derived from bootstrap samples of the UKPDS trial population which were generated by sampling with replacement from the original data set. When the desired number of bootstraps has been chosen, each bootstrap run will use a different set of model equation parameters, drawing from those available. The current version of the software is limited to a maximum of 1,000 bootstraps. Ideally 1,000 bootstraps should be specified although 100 may be sufficient to

obtain approximate confidence intervals estimates". We used this function and chose 100 bootstraps, this enabled us to produce confidence intervals. Using more than 100 bootstraps caused EXCEL to freeze up for unknown reasons.

10.3.3. Unit costs and HRQoL data

Unit costs are an important input in modelling and vary across countries. In order to adapt the UKPDS Outcomes Model to the Norwegian setting we sought to use Norwegian specific cost data to the furthest extent. Some costs were derived from the physicians fee schedules and DRGs and finally some cost data are from the NORCAD manual (72).

In the table below the default costs and utility decrements in the UKPDS Outcomes Model are shown alongside our best estimates of the same in the Norwegian setting. The default UKPDS Outcomes Model costs (shown in the top-part of the table below) are converted from English pounds to Norwegian Kroner (NOK) using an exchange rate of 10. The utility decrements associated with a complication are mostly similar in both tables, but the initial utility value was set to another level based on findings in our own HRQoL study (Paper II).

Table 3 Unit costs (in our adaptation: 2009* costs (NOK)) and utility decrements (top part of table - default in the UKPDS Outcomes Model, bottom part of table - used in our adaptation)

DEFAULT IN THE UKPDS OUTCOMES MODEL					
Initial utility: 0.785**					
	At time of event			**In subsequent years**	
	Fatal	**Non-fatal**	**Utility decrement****	**Cost**	**Utility decrement****
Ischemic heart disease (IHD)		26 960	-0.090	8 910	-0.090
Myocardial infarction (MI)	13 660	51 990	-0.055	8 560	-0.055
Heart failure	30 070	30 070	-0.108	10 540	-0.108
Stroke	40 110	31 800	-0.164	6 010	-0.164
Amputation	103 540	103 540	-0.280	5 980	-0.280
Blindness		13 580	-0.074	5 750	-0.074
Renal failure	300 000	300 000	-0.263	300 000	-0.263
USED IN OUR ADAPTATION OF THE UKPDS MODEL					
Initial utility: 0.850[a]					
Ischemic heart disease (IHD)		83 240[b]	-0.090[c]	4 390[b]	-0.090[c]
Myocardial infarction (MI)	42 749[b]	101 234[b]	-0.055[c]	3 509[d]	-0.055[c]
Heart failure	29 596[b]	29 596[b]	-0.108[c]	27 094[b]	-0.108[c]
Stroke	180 000[b]	180 000[b]	-0.164[c]	84 297[e]	-0.164[c]
Amputation	113 390[f]	113 390[f]	-0.280[c]	95 000[g]	-0.280[c]
Blindness		69 425[h]	-0.074[c]	889[i]	-0.074[c]
Renal failure	49 461[j]	577 382[k]	-0.263[l]	577 382[k]	-0.263[l]

* Some cost elements (fees) are from 2008. This is considered to make no noticeable impact on results
**The UKPDS Outcomes Model assume that utility value decrements for multiple co-morbidities are additive (example: the utility of a patient who had other IHD and then had an MI would first be decremented by 0.090 and then by a further 0.055). The utility decrements are permanent, lasting for the remaining life years.
[a] Solli O, Stavem K, Kristiansen IS: Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. *Health Qual. Life Outcomes* 8:18, 2010
[b] Wisløff T, Selmer RM, Halvorsen S, and Kristiansen IS. Norwegian Cardiovascular Disease Model (NorCaD) – a simulation model for estimating health benefits and cost consequences of cardiovascular interventions. 2008. Oslo
[c] Default in the UKPDS Outcomes Model. Source: Clarke P., Gray A. & Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62) Medical Decision Making (2002); 22: 340-349
[d] Assumption: Per year: 4 GP visits (NOK289 per visit, source: Fee Schedule for GP's), lipid and enzyme tests at each visit (NOK212 per test, source Fee Schedule for GP's) and assumed usage of statins, antihypertensives and acetylsalicylic acid.
[e] Adapted from Fjærtoft H, Indredavik B, Magnussen J et al. Early supported discharge for stroke patients improves clinical outcome. Does it also reduce use of health services and costs? *Cerebrovasc Dis* 2005; 19: 376 - 83.
[f] DRG113
[g] Tennvall GR, Apelqvist J, Eneroth M.: Costs of deep foot infections in patients with diabetes mellitus. *Pharmacoeconomics.* 2000 Sep;18(3):225-38.
[h] Assumption: One hospital admission for eye disease (DRG46+47, NOK19,347), two follow-up visits with ophthalmologist (NOK889 per visit, source Specialist Fee Schedule) and 0.5 information/course for patients with blindness in one eye (NOK2,300 per day, assumed length 42 days).
[i] Assumption: Per year, one specialist consultation (NOK889 per visit, source Specialist Fee Schedule)
[j] DRG 317
[k] DRG 316x3x52
[l] Default in the UKPDS Outcomes Model. Source: Kiberd BA & Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation *BMJ* 1995; 311 (702) 1595-1599

The UKPDS Outcomes Model estimates the risk of complications and the associated costs and utility decrements. The model does not capture the cost of treating diabetes (insulin, oral glucose lowering drugs, diabetes equipment, etc) or diabetes related costs (nutrion counselling, lifestyle interventions, etc.). We captured such costs in a separate EXCEL spreadsheet model, alongside the UKPDS Outcomes Model. Our estimated cost data from this spreadsheet are shown in the table below.

Table 4 Estimated costs of insulin, oral glucose lowering drugs, diabetes equipment and the lifestyle intervention (2009) Norwegian Kroner (NOK)

Cost type	*Per patient per year (NOK)**
DIRECT COSTS	
Insulin (excl. VAT)	5 300**
Equipment associated with insulin use	7 234***
Oral glucose lowering drugs (excl. VAT)	908**
GP visits and checkups	1 542
Overhead Lifestyle intervention	
Medical doctor monitoring	389
Invitations/information	1 111
Lifestyle intervention – diet	
Nutritionist guidance group meetings	2 302
Nutritionist guidance individual session	2 960
Transportation to sessions and meetings	640
Lifestyle intervention – exercise	
Trainer/Coach	3 733
Transportation to exercise	3 200
Subtotal direct costs	**29 319**
INDIRECT COSTS (loss of leisure or working hours)	
Lifestyle intervention – diet	
Nutritionist guidance group meetings	17 640
Nutritionist guidance individual session	2 520
Lifestyle intervention – exercise	
Exercise sessions	100 800
Subtotal indirect costs	**120 960**
Total costs (direct + indirect) year 1	**150 279**
Total costs (direct + indirect) year 2****	**148 779**
Total costs (direct) year 1	**29 319**
Total costs (direct) year 2****	**27 819**

* 9 patients in the lifestyle program
** Based on numbers from 2008. Numbers from 2009 were not available at the time.
*** Based on numbers from 2005. Numbers from 2005 were collected for Paper I.
**** Undiscounted

The numbers in the table above are based on information in the Aas study and assumptions about the costs of the lifestyle program. Costs of medicines and medical equipment were taken from different years available at the time. Calculations and assumptions of costs in the table above are shown in the table below.

Table 5 Assumptions and calculations - costs of insulin, oral glucose lowering drugs, diabetes equipment and the lifestyle intervention (costs shown in table 4)

Cost type	*Source*	*Calculation*
DIRECT COSTS		
Insulin (excl. VAT)	NorPD*	Total sale of ATC A10A/Number of users in 2008, multiplied with 0.8 to remove VAT – ((337,688,416/50,971)*0.8)
Equipment associated with insulin use	NLWA**, NorPD*	Total expenditure on diabetes equipment (reimbursement and patient co-payment)/ Number of users of insulin in 2005 - (340,516,405/47,074)
Oral glucose lowering drugs (excl. VAT)	NorPD*	Total sale of ATC A10B/Number of users in 2008, multiplied with 0.8 to remove VAT – ((119,398,952/105,192)*0.8)
GP visits and checkups	Assumptions	Assume 3 GP-visits per year, cost per GP-visit NOK300,-, assume: 1 creatinine, 1 HbA1c, 1 cholesterol, test per visit at NOK50,-, NOK50,-, NOK114,-, respectively – (300 + 50 + 50 + 114 = 514), (514 x 3 = 1,542)
Overhead Lifestyle intervention		
Medical doctor monitoring	Assumptions	Medical Doctor salary per hour NOK500,-, multiplied by 1.4 to include social costs, 5 hours in total for the lifestyle programme = NOK3,500,-. 9 patients. Cost per patient: NOK389,-.
Invitations/information	Assumptions	Assume NOK10,000 for the programme. 9 patients. Cost per patient: NOK1,111,-.
Lifestyle intervention – diet		
Nutritionist guidance group meetings	Assumptions	Assume yearly salary of NOK450,000, multiplied by 1.4 to include social costs, 1,700 work hours per year, 14 meetings per year, 4 hours in total for preparation and group meetings. Divided by 9 patients.
Nutritionist guidance individual session	Assumptions	Assume yearly salary of NOK450,000, multiplied by 1.4 to include social costs, 1,700 work hours per year, 2 sessions per year, 4 hours for preparation and session.
Transportation to sessions and meetings	Assumptions	Assume all meeting/sessions arranged locally and transport is per subway, tram or bus. NOK20,- per trip (one way), 14 meetings, 2 sessions.
Lifestyle intervention – exercise		
Trainer/Coach	Assumptions	Assume salary per hour NOK300,-, multiplied with 1.4 to include social costs. 40 weeks of exercise, 2 sessions per week. Divided by 9 patients.
Transportation to exercise	Assumptions	Assume all arranged locally and transport is per subway, tram or bus. NOK20,- per trip (one way), 80 exercise sessions.
INDIRECT COSTS (loss of leisure or working hours)		
Lifestyle intervention – diet		
Nutritionist guidance group meetings	Assumptions	Assume cost per hour to NOK300,-, multiplied by 1.4 to include social costs. 14 meeting per year, time spent for each meeting 3 hours (transportation and participation).
Nutritionist guidance individual session	Assumptions	Assume cost per hour to NOK300,-, multiplied by 1.4 to include social costs. 2 sessions per year, time spent for each meeting 3 hours (transportation and participation).
Lifestyle intervention – exercise		
Exercise sessions	Assumptions	Assume cost per hour to NOK300,-, multiplied by 1.4 to include social costs. 80 exercise sessions per year, time spent for each session 3 hours (transportation and participation).

*Norwegian Prescription Database
**Norwegian Labour and Welfare Administration

In the UKPDS Outcomes Model, the risk of complications is handled probabilistically while the unit costs are fixed (without distributions or uncertainty). The uncertainty in the risk of complications including death is expressed in the 14 risk equations (see appendix 5-7). To capture uncertainty in the intervention costs, we combined output from Monte Carlo simulation in the UKPDS model with estimations in a separate spreadsheet. UKPDS first provided 500 simulations of complication costs, life expectancies and QALYs for each of the two patient groups (two-year lifestyle intervention versus insulin treatment). The intervention costs were made dependent on the life expectancies returned by the UKPDS Outcomes Model. Furthermore, the intervention costs were made probabilistic in a separate EXCEL spreadsheet. We utilized the inverse gamma function in EXCEL, a random numbers generator (between zero and one) and an assumed standard deviation of plus/minus 10 percent of the intervention cost (adjusted for life expectancy). EXCEL then drew from a gamma distribution for each of the intervention cost estimates. For each of the iterations from the UKPDS Outcomes Model the intervention cost estimates were added to the complication costs. The sets of QALYs and total costs (intervention costs and complication costs) for the two-year lifestyle group and the insulin group) provided us with data which enabled us to perform a probabilistic sensitivity analysis (Online Appendix A7, Paper III).

10.4. Ethical considerations

The survey and the questionnaire were approved by the Norwegian Social Science Data Services and the Regional Committee for Ethical Research. Handling of the data was done according to the guidelines of the Norwegian Social Science Data Services and the Regional Committee for Ethical Research. Anonymity of respondents was secured by connecting numbers to the addresses and only registering the numbers in the database. The

list connecting addresses to the numbers was stored separated from the file with respondent answers. Destruction of the list of addresses ensured anonymity.

11. RESULTS

A full description of demographic features of the survey sample used in Paper I and Paper II are shown in table 1, Paper II.

11.1. Costs of diabetes in Norway

11.1.1. Direct costs

In 2005, there were 8,900 hospital stays with diabetes as the main diagnosis at an estimated total cost of NOK178 million (see table 1, Paper I). Approximately 65% of the costs were attributable to insulin dependent diabetes and 27% to non insulin dependent diabetes. Additionally, there were 53,000 hospital stays with diabetes as a secondary diagnosis accounting for NOK2 billion in costs. The most frequent main diagnoses when diabetes was a secondary diagnosis were cardiovascular diseases (31% of costs), malignancies (12%) and respiratory diseases (11%).

Of the secondary diagnoses, type 2 diabetes (E11) accounted for 65%, while type 1 (E10) accounted for 34%.

We explored regional differences in the data provided by Norwegian patient register and found that the diabetes related in-hospital costs per inhabitant were 27% higher in the geographic region with the highest costs compared to region with the lowest when accounting for admissions with diabetes as main and secondary diagnosis. The total national in-hospital costs would be NOK2.6 billion if all regions had the same cost level as the most costly, 15% more than the numbers presented in table 1, Paper I.

The costs related to out-patient clinic visits in hospitals amounted to NOK67 million (table 2, Paper I).

The cost of services from GPs and emergency units was NOK122 million (table 2, Paper I) including home visits for hypoglycaemia. The cost relating to private practicing

specialists amounted to NOK22 million. On the basis of the survey of diabetes, the estimated annual number of physician home visits for hypoglycaemia was 7,800 at a cost of NOK4.6 million. Type 1 diabetes accounted for 58% and type 2 diabetes for 42% of the visits.

The cost of hypoglycaemic agents for treating diabetes was NOK420 million (18% of total costs) (table 4, Paper I) of which NOK298 million (70%) represented insulin and analogues (A10A) and the rest oral glucose lowering drugs (A10B). Within the insulin group the cost of intermediate-acting insulin (A10AC) was NOK130 million and fast-acting insulin (A10AB) was NOK106 million. In the group of glucose lowering drugs (A10B) the cost of sulphonamides, urea derivatives (A10BB) was NOK53 million and biguanides (A10BA) NOK40 million. In the patient survey, the use of antihypertensive drugs was reported by 30% of the type 1 diabetes individuals (NOK10 million) and 64% of the type 2 diabetes group (NOK84 million), while the proportions for cholesterol lowering drugs were 26% (NOK20 million) and 60% (NOK182 million), respectively.

Expenditure on diabetes related medical equipment was NOK340 million (Table 8, Paper I). The largest component here was glucose tests accounting for NOK268 million (80% of the total). Lancets for blood sampling accounted for approximately NOK50 million, (13% of the total).

Among costs estimated on the basis of the patient survey (table 4, Paper I), physiotherapy accounted for NOK131 million, foot therapy NOK78 million, acupuncture NOK39 million and nutrition guidance NOK12 million.

11.1.2. Indirect costs

The costs related to sick leave were NOK141 million (Table 7, Paper I) of which type 2 diabetes accounted for 85%.

Total costs related to time limited disability support and disability pensions amounted to NOK410 million (Table 9, Paper I), of which disability pensions accounted for NOK394 million (96%).

Cost of basic and supplemental benefits was estimated at NOK45 million (Table 9, Paper I).

11.1.3. Total costs

Total costs were NOK2.3 billion (table 2, Paper I) when hospital stays with diabetes as secondary diagnoses were excluded and NOK4.35 billion when they were included. The largest component was medicines with NOK717 million (31% of the total). The second largest was disability pensions with NOK410 million (18%). Medical devices contributed NOK340 million (15%) and hospital admissions NOK178 million (8%).

11.2. Determinants of health-related quality of life among persons with diabetes

11.2.1. Health-related quality of life and utility scores

In total 10% of type 1 diabetes patients had problems with MOBILITY as judged from the EQ-5D, 3% with SELF-CARE, 19% with USUAL ACTIVITES, 34% with PAIN/DISCOMFORT and 35% with ANXIETY/DEPRESSION (table 2, Paper II). For Type 2 diabetes the numbers were 26%, 6%, 25%, 45% and 33%, respectively. The mean EQ-5D index score was 0.83 (SD=0.24) in type 1 diabetes and 0.81 (SD=0.22) in the type 2 (p=0.32). For respondents without reported complications, the mean EQ-5D index scores were 0.90 in type 1 diabetes and 0.85 in type 2 diabetes (table 3, Paper II). Presence of one complication decreased values to 0.76 and 0.80. With 2 or more diabetes-related complications values were 0.55 and 0.64.

11.2.2. Regression analyses

In the binary logistic regressions of type 1 diabetes on EQ-5D dimension responses (table 4, Paper II), ischemic heart disease, foot ulcer, neuropathy, body mass index and receiving help from others were statistically significant determinants for reporting problems in the MOBILITY dimension. None of the covariates had impact on the SELF-CARE dimension. Disability pension and limitations at work had an impact on the USUAL ACTIVITIES dimension. Age, ischemic heart disease and neuropathy had an impact on the PAIN/DISCOMFORT dimension, and age, impaired vision, ischemic heart disease, neuropathy and fear of hypoglycaemia had an impact on the ANXIETY/DEPRESSION dimension. For type 2 diabetes (table 5, Paper II) age, impaired vision, stroke, neuropathy, body mass index and receiving help from others were statistically significant determinants of MOBILITY. Receiving help from others was a statistically significant determinant for SELF-CARE. Sex, stroke, disability pension, receiving help from others and limitations at work were associated with USUAL ACTIVITIES. Ischemic heart disease, neuropathy and hypoglycemia had an impact on PAIN/DISCOMFORT. Age, foot ulcers, number of hospital admissions during the previous 6 months and fear of hypoglycemia were associated with ANXIETY/DEPRESSION scores.

The tables below show the results from the analyses we performed initially with the stepwise approach while Tables 4 and 5 of paper II shows the full models.

Table 6 Binary multivariate logistic regression of responses to the EQ-5D items in type 1 diabetics, odds ratios (95% CI)

	EQ-5D dimensions				
	Mobility	**Personal care**	**Usual activities**	**Pain and discomfort**	**Anxiety and depression**
Sex (male=0, female=1)	OM	OM	OM	0.45 (0.21 – 0.97)*	OM
Age (in 10 years)	OM	OM	OM	1.30 (1.01 – 1.68)*	0.71 (0.54 – 0.93)*
Impaired vision (no=0, yes=1)	OM	11.02 (1.07 – 113.80)*	OM	-----	3.98 (1.58 – 10.01)**
Ischemic heart disease (no=0, yes=1)	22.35 (5.24 – 95.38)***	OM	OM	6.74 (1.57 – 28.92)*	6.49 (1.43 – 29.42)*
Impaired kidney function (no=0, yes=1)	-----	-----	-----	-----	OM
Foot Ulcer (no=0, yes=1)	13.55 (1.77 – 103.45)*	OM	-----	OM	OM
Stroke (no=0, yes=1)	OM	OM	OM	OM	OM
Neuropathy (no=0, yes=1)	10.67 (2.22 – 51.38)**	OM	-----	33.24 (3.88 – 284.79)**	4.24 (1.03 – 17.44)*
Body mass index (kg/m^2)	OM	-----	-----	-----	-----
Disability pension (no=0, yes=1)	-----	-----	5.21 (2.07 – 13.15)***	-----	-----
Number of hospital admissions during previous 6 months	-----	-----	-----	-----	OM
Receives help from others (no=0, yes=1)	-----	19.05 (1.86 – 194.73)*	5.06 (1.71 – 14.98)**	-----	-----
Hypoglycaemia index#	-----	-----	-----	OM	OM
Fear of hypoglycaemia## (small=0, large=1)	-----	-----	-----	-----	4.12 (1.93 – 8.80)***
Limitations at work## (small=0, large=1)	-----	-----	9.22 (3.21 – 26.51)***	-----	-----
Limitations socially## (small=0, large=1)	-----	-----	OM	-----	-----
Log likelihood	-35.89	-13.85	-59.57	-88.31	-86.22

* p<0.05, **p<0.01, ***p<0.001. Cells with dotted line indicate that the variable was not included in the model. OM: omitted during regression modelling

Self reported episodes of hypoglycaemia, with 4 levels of severity (level 1 = hypoglycaemia cured with the intake of for example fluids containing sugar, no help from other required, level 2 = hypoglycaemia cured with the intake of for example fluids containing sugar, help from others required, level 3 = hypoglycaemia with help from doctor required (no hospital admission), level 4 = hypoglycaemia resulting in hospital admission), then added with severity weights (level 1 x 1, level 2 x 2, level 3 x 3, level 4 x 4) and finally divided in 3 groups 0, 1-11 and 12 to max

Self reported on a scale from 1 to 5 (1 = not at all, 5 = very much), recoded to 2 levels (> and < than 2.5 due to imputed values having values with decimals)

Table 7 Binary multivariate logistic regression of responses to the EQ-5D items in type 2 diabetics, odds ratios (95% CI)

	EQ-5D dimensions				
	Mobility	**Personal care**	**Usual activities**	**Pain and discomfort**	**Anxiety and depression**
Sex (male=0, female=1)	OM	OM	0.52 (0.29 – 0.96)*	OM	OM
Age (in 10 years)	1.44 (1.11 – 1.88)**	OM	1.39 (1.05 – 1.85)*	OM	OM
Impaired vision (normal=0, reduced=1)	3.22 (1.65 – 6.25)**	OM	OM	-----	OM
Ischemic heart disease (no=0, yes=1)	2.06 (1.04 – 4.11)*	OM	OM	2.86 (1.50 – 5.46)**	OM
Impaired kidney function (no=0, yes=1)	-----	-----	-----	-----	OM
Foot Ulcer (no=0, yes=1)	OM	OM	-----	OM	8.34 (2.06 – 33.71)**
Stroke (no=0, yes=1)	OM	OM	5.49 (1.80 – 16.78)**		OM
Neuropathy (no=0, yes=1)	11.44 (3.38 – 38.67)***	OM	-----	Predicts perfectly#	OM
Body mass index (kg/m^2)	1.11 (1.05 – 1.18)***	-----	-----	-----	-----
Disability pension (no=0, yes=1)	-----	-----	2.72 (1.40 – 5.26)**		-----
Number of hospital admissions during previous 6 months	-----	-----	-----	-----	1.70 (1.07 – 2.71)*
Receives help from others (no=0, yes=1)	-----	8.84 (3.49 – 22.39)***	5.67 (2.84 – 11.33)***	-----	-----
Hypoglycaemia index##	-----	-----	-----	1.68 (1.14 – 2.48)**	OM
Fear of hypoglycaemia### (small=0, large=1)	-----	-----	-----	-----	5.71 (3.46 – 9.41)***
Limitations at work### (small=0, large=1)	-----	----	7.61 (4.06 -14.26)***	-----	-----
Limitations socially### (small=0, large=1)	-----	----	OM	-----	-----
Log likelihood	-172.80	-69.17	-139.17	-234.44	-191.62

* p<0.05, **p<0.01, ***p<0.001, # All patients reporting neuropathy also reports having problems in the "pain and discomfort" dimension of the EQ-5D. Cells with dotted line indicate that the variable was not included in the model. OM: omitted during regression modelling

Self reported episodes of hypoglycaemia, with 4 levels of severity (level 1 = hypoglycaemia cured with the intake of for example fluids containing sugar, no help from other required, level 2 = hypoglycaemia cured with the intake of for example fluids containing sugar, help from others required, level 3 = hypoglycaemia with help from doctor required (no hospital admission), level 4 = hypoglycaemia resulting in hospital admission), then added with severity weights (level 1 x 1, level 2 x 2, level 3 x 3, level 4 x 4) and finally divided in 3 groups 0, 1-11 and 12 to max

Self reported on a scale from 1 to 5 (1 = not at all, 5 = very much), recoded to 2 levels (> and < than 2.5 due to imputed values having values with decimals)

In the linear regression of the EQ-5D index for type 1 diabetes, presence of ischemic heart disease had a negative impact (-0.181), along with stroke (-0.291), neuropathy (-0.358), receiving disability pension (-0.111) and social limitations (-0.107) (table 6, Paper II).

For type 2 diabetes the following conditions had a negative impact on the EQ-5D index (table 6, Paper II): stroke (-0.135), neuropathy (-0.187), disability pension (-0.100), receives help from others (-0.123), fear of hypoglycaemia (-0.078) and limitations at work (-0.087).

11.3. Cost-effectiveness analysis of a lifestyle intervention versus insulin

With immediate switch to insulin treatment, the estimated discounted life expectancy was 9.44 years (7.67 QALE), while it was 9.48 (7.71 QALE), 9.53 (7.75 QALE) and 9.64 (7.86 QALE) for two-year, five-year and lifelong lifestyle intervention (table 1, Paper III). The discounted lifetime total costs including indirect costs of the four programmes were, NOK283,637, NOK512,540, NOK799,245 and NOK1,417,004, respectively. Compared with scenario 1, the costs per incremental life year were NOK6,053,073, NOK6,209,362 and NOK5,832,427 for two-year, five-year and lifelong lifestyle intervention, respectively. Finally the costs per incremental QALY were NOK6,040,995, NOK6,350,144 and NOK5,863,067 for the respective courses of treatment.

The costs of the lifestyle program were estimated at NOK135,296 in the first year and NOK133,796 in the subsequent years. Costs were higher in the initial year due to the overhead costs of the program. Direct costs consisted of overhead costs NOK1,500, costs of running the diet part of the program (NOK5,902) and costs of the exercise program (NOK6,933). Indirect costs consisted of time to participate and travelling to the session and were estimated to be NOK20,160 for the diet sessions and NOK100,800 for exercise sessions.

The largest contributor to costs were indirect costs incurred by the patients' participation in diet and exercise sessions and time spent on travelling to these session. When indirect costs were set equal to zero, the estimated discounted total costs of the four

programmes were NOK283,637, NOK585,178, NOK288,125 and NOK290,142, respectively. The incremental analyses (each course compared with immediate switch to insulin) resulted in a costs per incremental life year of NOK40,738, NOK54,052 and NOK33,473 for two-year, five-year and lifelong lifestyle intervention, respectively (NOK40,656, NOK55,277 and NOK33,649 per QALY).

When the impact of the lifestyle program on HbA1c was increased with 5% for two-year, five-year and lifelong lifestyle interventions, the life expectancy and QALE's were 9.53 (7.75), 9.60 (7.82) and 9.69 (7.92) respectively. Immediate change to insulin was kept unchanged. This change led to an increase in life expectancy of 0.046 (16.9 days, 0.49%), 0.071 (26 days, 0.75%) and 0.054 (19.9 days, 0.56%) and QALY's of 0.046 (16.9 days, 0.60%), 0.069 (25 days, 0.89%) and 0.055 (20 days, 0.70%) for two-year, five-year and lifelong lifestyle program, in that order. With this increase in impact on HbA1c, the cost per QALY of NOK2,692,540, NOK3,451,426 and NOK4,580,114 for the two-year, five-year and lifelong programmes. Without indirect costs, all lifestyle programmes became dominant strategies (lower cost and better effect) when compared to immediate insulin.

12. DISCUSSION

12.1. Cost-of-diabetes in Norway

The results of the cost-of illness study clearly indicate that diabetes places a considerable financial burden on patients and the Norwegian society. The total costs of treating diabetes in Norway in 2005 amounted to about NOK2.3 billion or 1.3% of total health care expenditures, or 2.5% if all diabetes related hospital stays are included. Interestingly, patient expenditures for acupuncture, physiotherapy and foot therapy were many times those of nutritional guidance. In addition, diabetes imposes costs to society in terms of lost production from job absenteeism and premature mortality.

Two important issues to keep in mind when accounting for costs of diabetes are the assumed large number of individuals with type 2 diabetes that remain undiagnosed. The costs of these patients are not included in our estimates. Furthermore some studies point to the probability of diabetes being under-reported. One example is a resent Scottish study (73) which aimed to assess the completeness of coding of diabetes in hospital inpatient admissions. The study population was patients identified with diabetes prior to hospital admission. Data were derived from linking the Scottish National Diabetes Register and hospital admissions. The authors found that only 59% of hospital inpatient admissions for people previously diagnosed with diabetes mentioned diabetes as a diagnosis at discharge from hospital. Meanwhile, over 99% of people with hospital records stating diabetes were included in the diabetes register. Regarding diabetes as a co-morbidity, completeness varied by primary diagnosis, Admissions with coronary heart disease and cancer as the primary diagnosis mentioned co-existing diabetes in 70% and 41% of the cases, respectively. A conclusion in the study is that hospital data alone considerably

underestimates the number of admissions and bed days but overestimate length of stay for people with diabetes.

Our study results need to be viewed in the context of potential limitations: some costs may be underestimated, some costs may be overestimated and some costs are omitted. Most of the limitations were mentioned in Paper I, but some limitations were omitted or only briefly discussed due to space limitations. Of particular interest are indirect costs or production losses due to diabetes. We did not account for productions losses from diabetes-related premature mortality because we adopted the prevalence approach. Diabetes may reduce life expectancy (7), and premature mortality represents a considerable productivity loss.

In principle, a cost-of-illness analysis should provide an estimate of the diabetes-attributable costs. The World Health Organization has the following definition of attributable fraction (74): *"The contribution of a risk factor to a disease or a death is quantified using the population attributable fraction (PAF). PAF is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use)".* Because diseases may have many causes that interact, it is not easy to estimate the attributable fraction. The same type of arguments applies for the diabetes attributable costs (costs that would be avoided if all diabetes were eliminated). Even with precise estimates of all health care utilization with diabetes as a primary or secondary diagnosis, we cannot estimate the diabetes attributable costs because the diabetes related complications may have multiple causes.

Diabetes may cause complications such as cardiovascular disease, renal failure, retinopathy, erectile dysfunction and others that incur costs. It is not easy to capture all these costs unless diabetes is stated as a main or secondary diagnosis when such

complications are treated. To the extent diabetes is stated as a secondary diagnosis at discharge from hospital, such costs are included in the NOK4.3 billion estimate. With respect to some of the complications, however, there are many causal factors and no reliable data on the fraction attributable to diabetes.

When estimating the cost of in-hospital care on the basis of the main diagnosis, hospital stays will not be included in the cost analysis if the diabetes diagnosis is not stated. Because hospitals in Norway have partial DRG financing, the choice of primary diagnosis may be influenced by the financial consequences of choice. Such incentives, however, would imply that doctors are likely to look for secondary diagnoses in order to increase reimbursements. Clearly, if a patient has impaired glucose tolerance (IGT), but a diabetes diagnosis has not been made, the costs of IGT will not be included in our results. The results of a Norwegian study indicate that diabetes patients tend to have higher costs than the average patient within certain DRGs (75). To the extent that this is the case, our estimates are biased downward.

In 2011 the Norwegian Directorate of Health performed an internal revision of the coding of diagnoses in Norwegian hospitals[7]. The revision checked the agreement between reported codes to the Norwegian Patient Register and codes registered in electronic patient charts. 4000 in- and outpatient visits, from different hospitals in all health regions in Norway were selected at random. The revision found agreement between main diagnosis reported to the NPR and main diagnosis in patient charts, in 80.5 percent of the cases. Approximately half of deviations were unexplained and were scheduled for a follow up and control.

A lack of diabetes diagnosis may also bias costs related to disability pensions and sick leave, physician visits, out-patient clinic visits and certain other types of services

[7] www.helsedirektoratet.no/finansiering/medisinsk-koding-og-kodeverk/medisinsk-koding/Documents/nasjonal-internrevisjon-medisinsk-kodepraksis-oktober-2011.pdf

where the costing is based on diagnosis. Finally, costs based on patient reported use of care may be underestimated because patients do not recall all use of care.

We have included some types of costs that are rarely included in cost-of-diabetes studies, such as doctor home visits related to hypoglycaemia, nutritionist guidance, foot therapy, physiotherapy and acupuncture. We cannot attribute all costs gathered in the patient survey to diabetes. For example, there are reasons other than diabetes for having acupuncture. It should be noted also that the survey we undertook may not be entirely representative of the diabetes population in Norway, especially for type 2 diabetes. In conclusion, the cost data are likely to be complete for drugs and devices, while other estimates may be biased.

While several cost data are uncertain, some are likely to be complete and correct. The NLWA keeps account of reimbursement for diabetes related medical devices and these costs are likely to be complete. Also, drug costs are quite accurate because all pharmacies register prescriptions electronically and transfer their data to the central registry.

In economics, the term cost is related to the concept of opportunity cost (the value of the resources used in the best alternative project). Prices in a well functioning market are supposed to represent opportunity cost. In the area of health care, markets are not well functioning because of patients' lack of information and government interventions (public subsidies and monopoly because of patent protection). This means that few if any unit costs represent opportunity costs, but this fact applies to all cost-of illness studies.

Despite possible methodological weakness, this study provides some general lessons. First, the main direct cost-drivers from diabetes are hospital services, pharmaceuticals and medical devices. These services are reimbursed in part or in full by governments in most industrialised countries. Second, other types of services such as foot therapy, physiotherapy, and acupuncture may represent considerable costs, but often

receive only partial and sometimes no reimbursement by governments. In Norway, the use of foot therapy is paid entirely by the patient, while the cost of foot ulcer treatment and amputations is covered almost fully by the government. This may seem paradoxical as untreated foot ulcers may lead to infections and ultimately amputation. Finally, the study reveals a high level of spending on acupuncture compared to much lower spending on nutritional guidance. Given the importance of diet for the progress of the disease, this result is somewhat paradoxical and suggests that patients could benefit from a different spending pattern.

The hospital costs with diabetes as main diagnosis were twice as high for type 1 diabetes as for type 2. However, the high frequency of cardiovascular disease with type 2 diabetes as the secondary diagnosis group indicates that type 2 diabetes is a major cost driver. The use of antihypertensive and cholesterol lowering drugs in our survey supports this view.

The number of patients on oral glucose lowering drugs was almost twice the number of users of insulin and analogues. In terms of costs, the pattern was opposite in that the total cost of insulin and analogues was twice the cost of oral glucose lowering drugs. This indicates that treatment of type 2 diabetes becomes more costly with disease progression because insulin is increasingly prescribed with progression.

Our results are somewhat different from those reported elsewhere. In Sweden the estimated costs of hypoglycaemia related to type 2 diabetes was €14.10 per patient per year (76) while our data would suggest approximately €3 per patient. The Swedish costs are higher because of a higher reported prevalence of hypoglycaemia and the inclusion of indirect costs.

When comparing our results with those of other studies one should be aware of methodological differences. We used a prevalence approach while studies relying on an

incidence approach with prediction of future costs may yield higher values. Also, the method for valuing absence from productive work may have considerable impact on the results of cost-of-diabetes studies. Clearly, the more types of diabetes related costs that are included, the higher the estimated costs. A recent review (41) suggests that there is a general tendency, heavily influenced by cost components included in the estimates, for indirect costs to make up a slightly larger proportion of total costs than direct costs. In the studies reviewed, the proportion of indirect costs was in the range of 25-64%. The review suggests a number of potential improvements in cost-of diabetes studies: the use of disease specific attributable risk procedures, new approaches to elicit the impact of co-morbidities, better methods for capturing cost information from new sources such as databases of managed care organizations, use of national patient surveys, the development of standards for estimating the costs and explicitly reporting the purpose of the diabetes cost study.

As an example of the differences seen in cost-of-illness studies, a German study (20) found that in 2001 the direct costs of diabetes accounted for 14% of total health care expenditure. This study compared costs of diabetes with a matched control group, finding that excess cost of diabetes accounted for 6.8% of total health care expenditure. Medicines accounted for 22% of excess costs. Indirect costs were 48% of the costs included.

A study performed in Ireland (77) estimated that the costs of treating type 2 diabetes represented 4.1% of the total health care expenditure. Hospitalisations accounted for almost half of overall costs, while ambulatory and medicines costs accounted for 27% and 25%.

In a Swedish (19) study, the costs of diabetes amounted to 5.7 billion Swedish Kroner (SEK). Direct costs were estimated to be 43% of total costs. Hospital care estimates were based on main diagnosis and were the main component of direct costs. Indirect costs in the Swedish study were significantly higher than our findings in Norway. This may be a

result of differences in diagnosis setting. The Swedish study includes costs related to productivity losses caused by premature mortality. The average age of retirement in Norway is around 60 (78). It seems unlikely that a significant number of diabetics die before this age.

In conclusion, the cost consequences of diabetes seem to be smaller in Norway than what has been observed in some other countries. The question is whether such differences are due to underestimations in this study, overestimation in other studies or real cost differences. It may be worthwhile noting that Norway generally has good register data, and it is not obvious that data limitations are less in other countries.

12.2. Health-related quality of life in diabetes

In this study, diabetics with complications had considerably reduced HRQoL, even though the impact on HRQoL was somewhat different for type 1 and type 2 diabetes. Stroke and neuropathy seem to have negative impact on overall HRQoL in both types of diabetes, while ischemic heart disease and social limitations impact on type 1 diabetes and fear of hypoglycaemia and limitations at work seem to impact negatively on type 2 diabetics. Being on disability pension is associated with reduced HRQoL in both types of diabetes, while receiving help from other people is significant only in type 2 diabetes.

Persons with type 1 diabetes reported more problems in the PAIN/DISCOMFORT and ANXIETY/DEPRESSION dimensions than persons with type 2 diabetes, while in the MOBILITY, SELF-CARE and USUAL ACTIVITIES dimensions the pattern seemed to be opposite.

Some limitations of the study should be noted. The respondents in the survey may not be representative of the diabetes population. A large proportion of the persons with type 1 diabetes in Norway (approx. 20,000) are members of the NDA while only a smaller

proportion of the type 2 (approx. 100,000) diabetics are registered. Clearly, our study does not capture HRQoL in undiagnosed diabetes patients. In line with other patient surveys, we had 40% non-response.

Lacking a Norwegian EQ-5D tariff we used the UK tariff (25;79). This tariff is probably the most commonly used EQ-5D tariff globally, and quite similar to the Danish (80) and US (54;55) ones. Also, one small Norwegian study indicates that UK and Norwegian values are quite similar (81).

In spite of the limited descriptive system of the EQ-5D, the instrument captures the impact of several diabetes complications both with respect to each of the dimensions and the EQ-5D index (Table 4, 5 and 6, Paper II). Ischemic heart disease, stroke and neuropathy, in particular, have a significant impact. Surprisingly, impaired vision had no impact on the MOBILITY dimension for persons with type 1 diabetes.

In our study, persons with type 1 diabetes had higher HRQoL than those with type 2. This is plausible because the former were younger. Interestingly, the difference was opposite in those with complications, and it seems as if diabetic complications have more impact on HRQoL in type 1 diabetes than type 2.

Some other studies have used the EQ-5D in populations with diabetes. In the UKPDS 37 study (82) persons with type 2 diabetes and no complications had a mean EQ-5D index value of 0.83 while we found 0.85. For type 2 patients with complications, our observed EQ-5D index value (0.73) was equal to that of the UKPDS 37 study. Taking into account that patient characteristics were similar in the UKPDS and our study, UK diabetes studies may be transferable to the Norwegian setting.

In another UK study (83) (only type 2 diabetes) the change in utility associated with fear of hypoglycaemia was relatively small compared to the disutility for serious diabetic complications such as neuropathy. Similarly, in our study fear of hypoglycaemia caused a

fairly small reduction in utility of 0.021 (type 1 diabetes) and 0.078 (type 2), but the disutility of neuropathy was larger with 0.358 (type 1 diabetes) and 0.187 (type 2 diabetes).

In a US review (84) of body weight and HRQoL in type 2 diabetes, the authors found decreasing HRQoL with increasing body weight in all included studies. When adjusting for other explanatory variables, we observed no significant impact of BMI on HRQoL.

A subgroup of unspecified type diabetics (n=117) in a Swedish general population EQ-5D study (85) (UK tariff) reported a higher frequency of problems in all dimensions of the EQ-5D, than in both diabetes categories in our study. Further, the Swedish diabetics had a lower mean EQ-5D index (0.74) than we observed in both type 1 and type 2 diabetes.

Diabetes complications may have an impact on many dimensions of quality of life, and the impact may be substantial. The strongest determinants of reduced HRQoL among persons with diabetes were ischemic heart disease, stroke and neuropathy.

12.3. Cost-effectiveness of lifestyle intervention in diabetes

Paper III indicates that lifestyle interventions are not cost-effective unless society disregards indirect costs. Compared with immediate switch to insulin treatment, the costs per incremental QALY were NOK6.041 mill, NOK6.350 mill and NOK5.863 mill for the two-year, five-year and lifelong lifestyle intervention (Table I, Paper III). When the cost of time related to travel and participation in the diet and exercise sessions were disregarded, the costs per incremental QALY for the respective treatment courses were NOK40,656, NOK55,277 and NOK33,649 (Table I, Paper III).

The strengths of the study lies in the use of real life clinical trial data and a well documented economic model (23). A limitation in our study is that the UKPDS Outcomes Model does not account for changes in BMI because weight was not a significant predictor

in the underlying regression analyses. In fact, body weight had an impact on the probability of having heart failure, only, and the effect was relatively small (23). We accounted for changes in body weight by applying a reduced weight throughout the remaining life years in all lifestyle intervention programmes, and this assumption will favour the lifestyle interventions.

Unfortunately, the ILIP trial did not report values for HbA1c, total and HDL cholesterol, HDL or systolic blood pressure at the time of diagnosis of type 2 diabetes. Lacking these data we used data from entry into the ILIP trial as a proxy for values at diagnosis. This assumption may be realistic because these patients are likely to be poorly controlled both at the time of diagnosis and when the next step is administering insulin (similar to patients at inclusion in the study). Patients who sign up for participation in lifestyle interventions programs are likely to be highly motivated and may not be representative of the average diabetes population. This, however, may not be a significant weakness of this economic study because lifestyle intervention should only be offered to highly motivated individuals. Some costs, however, may be incurred by the search for such motivated patients.

The UKPDS Outcomes Model is based on data from an intervention study performed up to 30 years ago. The relationship between diabetes complications and their predictors may therefore have changed considerably over time and place (UK versus Norway). Some or all of the risk equations may therefore be somewhat outdated. For instance the model may not take into account the full benefits of the effect statins have had on population cholesterol levels and thus risk of developing heart disease. This will however benefit all groups and may not cause major bias in the modelling results. The use of UK rather than Norwegian risk data may also represent a limitation.

Few economic studies of lifestyle intervention for diabetes have been published. In a Dutch study, the long term cost-effectiveness of lifestyle interventions for manifest type 2 diabetes was modeled [21] based on different clinical trials. The average gain in QALYs gain ranged from 0.01 to 0.14. In our study, QALY ranged from 0.04 for the two-year lifestyle intervention program to 0.19 for the lifelong lifestyle intervention program. The Dutch study only took direct costs into account and concludes that lifestyle interventions are likely to "yield important health benefits at reasonable costs", which is in line with our study when we disregard indirect costs. The authors state that essential evidence for long-term maintenance of health benefits was limited and that future research should be focused on long-term effectiveness of such programs.

The Diabetes Prevention Program (DPP) in the US (86), including metformin and intensive lifestyle interventions seems to reduce the incidence of type 2 diabetes compared with a placebo intervention. A study based on the DPP (87), indicate that the lifestyle and metformin interventions were cost-effective relative to placebo intervention. Both direct and indirect costs were taken into account in this study.

12.4. General discussion

The findings of these studies (Paper I-III) indicate that diabetes is a costly disease for both society and the individual with diabetes. The expected increase in prevalence of type 2 diabetes caused by aging population and increasing body weight in most industrialised countries should alarm decision makers of increasing costs in the future. Diabetes is a global and national challenge for populations, health care systems and budgets.

Viewing diabetes from a global perspective, the World Health Organization published in 2010 the Global status report on non-communicable diseases (NCD) (88). Almost 36 million of the 57 million global deaths in 2008 were a result of NCDs. Diabetes

accounted for 1.3 million deaths and is listed among the main NCDs along with cardiovascular diseases, cancers and chronic lung diseases. The three latter accounted for 17, 7.6, 4.2 million deaths, respectively. Tobacco, alcohol use, unhealthy diet, too little physical activity are claimed to be leading causes of NCDs. The report claims that interventions on population level may reduce the impact of NCDs, and highlights measures such as increasing tobacco and alcohol, tobacco control and reducing salt consumption. The report claims that heart disease, stroke and diabetes cause large reductions in national income each year, and furthermore that economic analyses have indicated that a 10% rise in NCDs may annually impact economic growth rate with a reduction of 0.5%. The report has a strong emphasis on prevention and early detection. This is to avoid progression to more severe and costly disease, and the lurking complications. For diabetes the following interventions are suggested: blood pressure control, glycaemic control and foot care. The reports project a large increase in global burden of NCDs in the coming decades.

Our studies are performed in the context of Norway and our local challenges. The results of the studies we have performed provide information on the complex cost structure of diabetes. Furthermore we have found that the complications ischemic heart disease, stroke and neuropathy are what decreases HRQoL most in groups of individuals with diabetes. Finally we observe that an intensive lifestyle program may be an alternative to insulin treatment in highly motivated groups, but whether such interventions are cost-effective is largely depending on how indirect costs are considered. Another challenge is how to recruit motivated patients.

The findings in our survey indicate that there is little emphasis on nutritional guidance and advice among individuals with diabetes. It seems paradoxical that large resources are used for treating complications associated with diabetes while prevention has

less emphasis and is not reimbursed. Another example of this paradox lies in the fact that foot-therapy is not publicly funded while amputations are.

The Norwegian association of GP's (NSAM) expresses concerns in their guidelines (89) regarding the increasing prevalence of obesity in Norway, not least among immigrant groups in which up to 55% of women are obese. The guidelines recommend lifestyle changes with change in diet and physical activity. Even though such recommendations may be reasonable, they may not be cost-effective. Our study indicates that *individual* interventions are cost-effective only if we disregard the cost of time and lost productivity. This is in line with a previous study of prevention of cardiovascular disease (90). Here, the authors conclude that individual based prevention is not cost-effective while interventions targeting groups of individuals are. Society may do well in considering more large scale, population based interventions aimed at prevention of diabetes. One example of such a population is immigrant women. In other areas of medicine we have seen how information and added knowledge have managed to change the attitude towards certain kinds of foods. One example is the changed view on fat and the moving-away from trans-fat and saturated fat during the last 30-40 years. In Norway, cardiovascular mortality is now less than 50% of what it was 30 years ago[8]. Even though some of this improvement is attributable to better medical treatment, changes in lifestyle also play a role.

12.5. Need for further research

Countless scientific papers conclude that more research is needed even though "important findings have been reported in this study". This thesis is no exception. The high costs of diabetes care may in itself indicate that more research is needed. The main argument in favour of more research does not lie in lowering of the diabetes costs. In fact, advances in

[8] Public Health Report, the Health State in Norway, Norwegian Institute of Public Health, Oslo, 2010.

health care are usually entailed by increased costs. The main argument lies in a better life for the patients: Less symptoms and complications and longer life – in other words more QALYs.

The findings in our research point to two main areas of research in Norway and elsewhere. First, society needs more information on interventions that can prevent the development of diabetes and its complications. Even though lifestyle interventions are seen as the cornerstone of diabetes treatment, the evidence that such interventions are effective is more limited. Not least, there is a need for long term follow up of patients in such trials. Second, there is a need to develop better and more up to date economic models of diabetes. Even though the UKPDS Model is based on a large trial, its parameter values may be outdates due to more use antihypertensive and lipid lowering drugs. Here, the Nordic countries could and should play a role because of the access to high quality register data. The HUNT study is an example of what potentials Nordic epidemiology has (91-109). By means of clinical trials and economic evaluation, policy makers may be able to develop sustainable policies to handle the increasing challenge of diabetes.

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PAPERS I, II AND III

I

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RESEARCH ARTICLE Open Access

Diabetes: cost of illness in Norway

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Abstract

Background: Diabetes mellitus places a considerable burden on patients in terms of morbidity and mortality and on society in terms of costs. Costs related to diabetes are expected to increase due to increasing prevalence of type 2 diabetes. The aim of this study was to estimate the health care costs attributable to type 1 and type 2 diabetes in Norway in 2005.

Methods: Data on inpatient hospital services, outpatient clinic visits, physician services, drugs, medical equipment, nutrition guidance, physiotherapy, acupuncture, foot therapy and indirect costs were collected from national registers and responses to a survey of 584 patients with diabetes. The study was performed with a prevalence approach. Uncertainty was explored by means of bootstrapping.

Results: When hospital stays with diabetes as a secondary diagnosis were excluded, the total costs were €293 million, which represents about 1.4% of the total health care expenditure. Pharmaceuticals accounted for €95 million (32%), disability pensions €48 million (16%), medical devices €40 million (14%) and hospital admissions €21 million (7%). Patient expenditures for acupuncture, physiotherapy and foot therapy were many times higher than expenditure for nutritional guidance. Indirect costs (lost production from job absenteeism) accounted for €70.1 million (24% of the €293 million) and included sick leave (€16.7 million), disability support and disability pensions (€48.2 million) and other indirect costs (€5.3 million). If all diabetes related hospital stays are included (primary- and secondary diagnosis) total costs amounts to €535 million, about 2.6% of the total health care expenditure in Norway.

Conclusions: Diabetes represents a considerable burden to society in terms of health care costs and productivity losses.

Background

Diabetes mellitus places a considerable burden on patients in terms of morbidity [1] and mortality [2] and on society in terms of costs [3-5]. The prevalence of type 2 diabetes is increasing in many countries [6] including Norway [7]. The number of patients with type 1 diabetes has been estimated at 25,000 [8]. In 2005, 117,600 persons in Norway were treated with insulin or oral antidiabetics [9]. We then assume that 92,600 of them have type 2 diabetes. In the Norwegian HUNT study [10] the proportion of patients with type 2 diabetes that was not on antidiabetic pharmaceuticals was 30%. This would imply that the total number of patients with type 2 diabetes is 132,300 (92,600/0.7) [8-11]. Additionally, a large number of persons with type 2 diabetes are assumed to be undiagnosed. It has been estimated that about 3-4% of the population above the age of 30 have type 2 diabetes [8].

Cost-of-illness analysis is a type of study that has been designed to quantify and value all economic consequences of a disease without taking into account the benefits of treatment. Therefore, cost-of-illness analysis in itself may not guide priority setting, but may be useful in designing financing systems and setting priorities for research.

There are two main approaches to cost-of-illness analysis: the prevalence [3,12-15] and the incidence [16] approach. The former accounts for all prevention, treatment and rehabilitation costs incurred during a given year, while the latter measures all such costs for new cases of the disease in a given year (the index year). Future treatment costs are accounted for by estimating the future costs for all individuals who develop the disease in the index year, and the present value of the

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costs are added to the costs incurred in the index year. The prevalence approach has the advantage of relating to measures of total annual health care expenditure, and it may yield more accurate estimates because it is based, at least in principle, on observed costs rather than projected ones. The advantage of the incidence approach lies in the fact that it provides projections of future costs that may be very different from current ones when incidence is increasing or declining. Such projections, however, may be uncertain.

The aim of this study was to quantify, using the prevalence approach, the societal costs in Norway of type 1 and type 2 diabetes, including indirect costs (productivity losses from diabetes).

Methods

The study was based on register data for the entire Norwegian population (n = 4.6 million). In addition we performed a survey of 584 persons with diabetes. We aimed at including all diabetes related costs, but some data were unavailable (e.g. depression, erectile dysfunction, neuropathic pain, osteoarthritis, congestive heart failure and pulmonary disease).

Direct costs

Direct costs are the costs of detection, treatment, prevention, rehabilitation and long-term care arising from an illness. In theory, all relevant health care and non-health care costs are included, but in practice there is a limit to what can be identified and measured. Data were, as far as possible, captured for 2005 and expressed in 2005 EURO (1 € ≈ 8.50 Norwegian Kroner).

Inpatient hospital services

From the Norwegian Patient Register (NPR) we obtained information on all hospital stays with the following ICD-10 codes as main or secondary diagnosis: E10 (insulin-dependent diabetes mellitus), E11 (non-insulin-dependent diabetes mellitus), E23.2 (diabetes insipidus), H28.0 (diabetic cataract), N08.3 (glomerular disorders in diabetes mellitus), O24 (diabetes mellitus in pregnancy), P70.0 (syndrome of infant of mother with gestational diabetes), P70.1 (syndrome of infant of a diabetic mother), P70.2 (neonatal diabetes mellitus), R73.0 (abnormal glucose tolerance test) and Z13.1 (special screening examination for diabetes mellitus). For each stay we obtained anonymous data on the primary diagnosis, secondary diagnosis, age, gender, geographic location, length of stay and DRG-weight. In Norway, patients receive a main diagnosis and possibly one or more secondary diagnoses at discharge from hospital. ICD10 has been used since 1999. On the basis of the diagnoses, age, sex and possibly procedures, patients are allocated to a diagnosis related group (DRG). The Directorate of Health performs annual cost studies of a representative sample of hospitals in order to estimate the mean hospital costs of patients in each DRG. Even though the cost estimate may be incorrect for the individual patient, on average they represent reasonable costs for the different types of patients. Hospital services are provided by five Regional Health Authorities, each with an independent board. Regional variation was analysed according to these units.

Outpatient clinic visits

Using the same ICD-10 codes as for inpatient services, data on the costs of outpatient clinic visits were provided by The Norwegian Labour and Welfare Administration (NLWA). No data for 2005 were available so data for 2006 were used. The NLWA data encompasses government reimbursements to hospitals. We added the standard patient co-payment per visit (€31). According to the financing model for hospitals, reimbursements and co-payments encompass 40% of the estimated outpatient clinic costs. The sum was therefore adjusted upwards by a factor of 2.5.

Physician services

Data on the use of general practitioner (GP) services and private specialists were obtained from NLWA. Claim forms, 90% of which are delivered electronically to NLWA, are provided with ICPC codes. We obtained data on all visits with ICPC codes T89 (insulin-dependent) and T90 (non-insulin-dependent) diabetes. For each patient contact, we obtained data on diagnosis, type of contact, reimbursement and patient co-payment.

Drugs

The Norwegian Prescription Registry (NPR) contains information on all prescriptions redeemed from pharmacies. We obtained data for 2005 on the following categories of ATC codes: A10A (insulin and analogues) and A10B (glucose lowering drugs). Additionally, we included the costs of patient reported use of antihypertensive drugs and cholesterol lowering drugs according to a patient survey (see "Other types of health care"). Based on data from the NPR we estimated average costs for one year of treatment with antihypertensive drugs (€154) and cholesterol lowering drugs (€357). This was based on market share of the different drugs available, average dose and prices.

Medical equipment

The NLWA keeps account of reimbursement for diabetes self-tests and insulin injection equipment (injection catheters, insulin pens and needles, syringes, lancets for blood sampling). To avoid double counting, the costs of insulin pumps were excluded. Insulin pumps are administered in hospitals and costs are captured in the DRG costing system.

Other types of health care

For various other types of resource use where register data are not available, we obtained information through

a self-administered questionnaire. A sample of persons with diabetes (n = 1,000) was randomly drawn from the membership file of the Norwegian Diabetes Association (36 000 members in 2006. This file is assumed to encompass most of the individuals in Norway with type 1 diabetes and about 15 000 with type 2 diabetes. We developed a comprehensive questionnaire in collaboration with persons with diabetes and doctors with diabetes care experience. The questionnaire was mailed to the sample patients in May 2007. Non-responders were followed up twice. Finally we had 584 responses that could be used in further analyses. The respondents were asked to state their use of the following types of health care services considered to be relevant among persons with diabetes for the previous three months: physiotherapy, acupuncture, nutrition counselling and GP home visits for hypoglycaemia. They were also asked questions about the duration of the diabetes, type of treatment and occurrence of diabetic related complications. To provide measures of the uncertainty of the estimates we derived confidence intervals by applying bootstrapping, 10 000 draws with replacement. The questionnaire was approved by Regional Committees for Medical Research Ethics and Norwegian Social Science Data Services. Treatment costs were estimated by assigning unit costs to the reported consumption of health care services. Unit costs were taken from professional organizations (physiotherapy, acupuncture) and GP's fee schedule [17].

Indirect costs

Lacking data on productivity losses from diabetes, we used payments of disability pension and economic support for diabetes related costs as a proxy for indirect costs. Disability pension and economic support are funded by the NLWA. We obtained data on all payments in 2005 for the ICD-10 diagnoses: E10, E11, E23.2, H28.0, H36.0, N08.3, O24, P70.0, P70.1, P70.2, R73.0 and Z13.1. A search was performed with all equivalent ICD-9 codes as well. Furthermore, the following ICPC codes were included: T89 (insulin-dependent diabetes mellitus), T90 (non-insulin-dependent diabetes mellitus), W85 (diabetes during pregnancy) and F83 (retinopathy).

Results

Inpatient hospital services

In 2005, there were 8 900 hospital stays with diabetes as the main diagnosis at an estimated total cost of €21 million (Table 1). About 65% of the costs were attributable to insulin-dependent diabetes and 27% to non-insulin-dependent diabetes. Additionally there were 53 000 hospital stays with diabetes as a secondary diagnosis accounting for €242 million in costs. The most frequent main diagnoses when diabetes was a secondary diagnosis were cardiovascular diseases (31% of costs), malignancies (12%) and respiratory diseases (11%). Of the secondary diagnoses, type 2 diabetes (E11) accounted for 65%, while type 1 (E10) accounted for 34%.

The diabetes related in-hospital costs per inhabitant were 27% higher in the geographic region with the highest costs compared to region with the lowest when accounting for admissions with diabetes as main and secondary diagnosis. The total national in-hospital costs would be €302 million if all regions had the same cost level as the most costly, 15% more than the numbers presented in Table 1.

Outpatient clinic visits

The costs related to outpatient clinic visits in hospitals amounted to €7.9 million (included in Table 2).

Physician services

The cost of services from GPs and emergency units was €14.4 million (Table 3) including home visits for hypoglycaemia. The cost relating to private practicing specialists amounted to €2.5 million. On the basis of the survey of persons with diabetes, the estimated annual cost of physician home visits for hypoglycaemia was €0.6 million (Table 4).

Table 1 Cost of in-hospital care according to diagnosis

Diabetes as main diagnosis	Number of hospital stays	Total (million €)
Type 1 diabetes*	5 813	13.5
Type 2 diabetes **	2 446	5.7
Other***	625	1.7
Total cost - main diagnosis	8 884	20.9
Diabetes as secondary diagnosis (ICD-10)	**Number of hospital stays**	**Total (million €)**
Infections (A00-A99+B00-B99)	1 686	9.3
Malignancies (C00-D89)	5 011	28.6
Neurological diseases (G00-G99)	1 401	4.2
Diseases of the eye (H00-H59)	1 405	2.3
Cardiovascular diseases (I00-I99)	14 545	74.2
Respiratory diseases (J00-J99)	4 504	25.8
Gastrointestinal diseases (K00-K93)	3 423	15.9
Musculoskeletal diseases (M00-M99)	2 777	16.4
Urinary tract diseases (N00-N99)	3 518	16.1
Other***	15 043	49.1
Total cost - secondary diagnosis****	53 313	241.8

* ICD-10 code E10, Insulin-dependent diabetes mellitus

** ICD-10 code E11, Non-insulin-dependent diabetes mellitus

*** ICD-10 codes E23.2, H28, N08.3, O24, P70.0, P70.1, P70.2, R73.0, Z13.1

**** Of the secondary diagnosis type 2 diabetes (E11) accounted for 65 percent, while type 1 (E10) accounted for 34 percent.

Table 2 Total cost of diabetes in Norway 2005

	Cost factor	Cost (million €)
Direct costs	In hospital care	20.9
	Outpatient care	7.9
	GP and emergency visits	14.4
	Private practicing specialist services	2.6
	Insulin and analogues (A10A*)	35.1
	Oral glucose lowering drugs (A10B*)	14.5
	Cholesterol lowering drugs	30.7
	Antihypertensive drugs	14.2
	Medical devices	40.1
	Nutritionist guidance	0.8
	Foot therapist	19.4
	Physiotherapy	16.5
	Acupuncture	5.3
	Subtotal	(76%) 222.4
Indirect costs	Sickness compensation	16.6
	Permanent disability pension and time limited disability pension	48.2
	Basic and/or supplemental benefits	5.3
	Subtotal	(24%) 70.1
	Total	292.5

Drugs

The cost of hypoglycaemic agents for treating diabetes was €49.6 million (17% of total costs) (Table 5) of which €35.1 million (70%) represented insulin and analogues (A10A) and the rest oral glucose lowering drugs (A10B). Within the insulin group the cost of intermediate-acting insulin (A10AC) was €15 million and fast-acting insulin (A10AB) was €12.5 million. In the group of glucose lowering drugs (A10B) the cost of sulphonamides, urea derivatives (A10BB) was €6.2 million and biguanides (A10BA) €4.7 million. For antihypertensive drugs the estimated cost was €1.2 and €13.0 million for type 1 and 2 diabetes, respectively, while it was €2.4 and €28.3 for cholesterol lowering drugs.

Medical equipment

Expenditure on diabetes related medical equipment was €40 million (Table 6). The largest component here was glucose tests accounting for €32 million (80% of the total). Lancets for blood sampling accounted for approximately €5.3 million, (13% of the total).

Other types of costs

Among costs estimated on the basis of the patient survey (Table 4), physiotherapy accounted for €18.8 million, foot therapy €20.8 million, acupuncture €5.7 million and nutrition guidance €0.9 million.

Table 3 Cost of physician services according to type of contact

	Surgery visits (million €)	Home visits (million €)	Other contacts (million €)	Total cost (million €)
GPs and emergency units				
Type 1 diabetes*	0.918	0.0349	0.1633	1.117
Type 2 diabetes **	11.646	0.1600	1.4341	13.240
Other***	0.044	0.0001	0.0104	0.054
Subtotal	12.608	0.1952	1.6078	14.411
Specialists in private practice				
Type 1 diabetes****	0.468	0.0000	0.0122	0.480
Type 2 diabetes*****	1.616	0.0007	0.0440	1.661
Retinopathy******	0.156	—	0.0006	0.156
Retinopathy*******	0.180	—	0.0004	0.180
Other********	0.069		0.0012	0.070
Subtotal	2.490	0.0007	0.0582	2.549
Total	15.098	0.1959	1.6660	16.960

* ICPC code T89, Insulin-dependent diabetes

** ICPC code T90, Non-insulin-dependent diabetes

*** ICPC codes F38 Retinopathy and W85 Diabetes during pregnancy

**** ICPC code T89 and ICD-10 code E10, Insulin-dependent diabetes

***** ICPC code T90 and ICD-10 code E11, Non-insulin-dependent diabetes

****** ICPC code F83 Retinopathy

******* ICD-10 code H36.0 Retinopathy

******** E23.2, H28.0, H36.0, N08.3, O24, P70.0, P70.1, P70.2, R73.0, Z13.1

Table 4 Costs of various other services*

	Resource use	Unit cost (€) per hour/ visit	Cost (million €) (95% CI)**
Type 1 diabetes	Hypoglycaemia - home visit	69	0.3 (0.1 - 0.6)
	Nutritionist guidance	21	0.1 (0.1 - 0.2)
	Foot therapist	53	1.4 (0.9 - 2.1)
	Physiotherapy	28	2.3 (1.2 - 3.4)
	Acupuncture	35	0.4 (0.1 - 0.8)
Subtotal	———		4.5
Type 2 diabetes	Hypoglycaemia - home visit	69	0.3 (0.0 - 0.4)
	Nutritionist guidance	21	0.8 (0.5 - 1.2)
	Foot therapist	53	19.4 (17.5 - 22.0)
	Physiotherapy	28	16.5 (11.3 - 21.3)
	Acupuncture	35	5.3 (2.6 - 10.6)
Subtotal	———		42.3
Total			46.8

* Data collected in the patient survey

** Confidence intervals based on bootstrapping

Indirect costs

The costs related to sick leave were €16.7 million (Table 7) of which type 2 diabetes accounted for 85%. Total costs related to time limited disability support and disability pensions amounted to €48.2 million (Table 8), of which disability pensions accounted for €46.4 million (96%). Cost of basic and supplemental benefits was €5.3 million (Table 9).

Total costs

Total costs were €293 million (Table 2) when hospital stays with diabetes as secondary diagnoses were excluded and €535 million when they were included. The largest component was medicines with €95 million (32% of the total). The second largest was disability pensions with €48 million (16%). Medical devices contributed €40 million (14%) and hospital admissions €21 million (7%).

Table 5 Cost of hypoglycaemic agents, cholesterol lowering drugs and antihypertensive drugs

	Number of users	Million DDD	Costs* (million €)
Insulin and analogues (A10A**) ***	47 073	28.9	35.1
Oral glucose lowering drugs (A10B**)***	85 014	36.2	14.5
Cholesterol lowering drugs****	85 880	—	30.7
Antihypertensive drugs****	92 172	—	14.2
Total	—	—	94.5

* Costs in terms of prices in Pharmacy sales prices including VAT

** ATC code

*** Data from the National prescription database

**** Data from a patient survey

Table 6 Cost of medical devices

	Reimbursement	Patient co-payment	Total Costs (million €)
Glucose tests	29.484	2.096	31.580
Lancets for blood sampling	4.885	0.378	5.262
Injection catheter	0.01	0.00024	0.010
Insulin pens	0.44	0.036	0.476
Needles for insulin pens	2.394	0,182	2.576
Insulin syringe	0.105	0.008	0.113
Urine test sticks	0.040	0.003	0.043
Total	37.358	2.703	40.061

Discussion

The results of this study clearly indicate that diabetes places a financial burden on the persons with diabetes themselves and furthermore the Norwegian public health care system. The total costs of treating diabetes in Norway in 2005 amounted to about €293 million or 1.4% of total health care expenditures [18], or 2.6% if all diabetes related hospital stays are included. Interestingly, patient expenditures for acupuncture, physiotherapy and foot therapy were many times that of those for nutritional guidance. In addition, diabetes imposes costs on society in terms of lost production from job absenteeism and premature mortality.

Cost-of-illness analyses in general should always be viewed in the context of potential limitations: some costs may be underestimated, some costs may be overestimated and some costs are omitted. Regarding our study, we have not accounted for productivity losses from diabetes-related premature mortality because we adopted the prevalence approach. In addition, diabetes may cause complications such as cardiovascular disease, renal failure, retinopathy, erectile dysfunction and others that incur costs. To the extent diabetes is stated as a secondary diagnosis at hospital discharge, such costs are included in the €535 million estimate. With respect to

Table 7 Cost of sick leave due to diabetes

Diagnose (ICPC)	Number of patients	Days of support	Payment (million €)
Insulin-dependent (T89)	269	17 602	1.6
Non-insulin-dependent (T90)	2 593	156 706	14.1
Retinopathy (F83)	149	7 948	0.8
Diabetes during pregnancy (W85)	38	1 523	0.13
Total	3049	183 779	16.7

Table 8 Cost of disability pension and time limited disability pension related to diabetes

	Benefit (€)	Number of patients	Expenditure (million €)
Time limited disability support	17 250	112	1.9
Disability pension	16 689	2 775	46.4
Total	16 711	2 887	48.2

some of the complications, there are many causal factors and no reliable data on the fraction attributable to diabetes.

When estimating the cost of in-hospital care on the basis of the main diagnosis (Table 1), some hospitals stays may be lost even when diabetes was the main cause of the stay. Because hospitals in Norway have partial DRG financing, the choice of primary diagnosis may be influenced by the financial consequences of choice of primary diagnosis. The results of a Norwegian study [19] indicate that diabetes patients tend to have higher costs than the average patient within certain DRGs. To the extent that this is the case, our estimates are biased. A lack of diabetes diagnosis may also bias costs related to disability pensions and sick leave, physician visits, outpatient clinic visits and certain other types of services where the costing is based on diagnosis. Finally, costs based on patient reported use of care may be underestimated because patients do not recall all use of care.

When including in-hospital care for stays where diabetes was a secondary diagnosis (Table 1), some stays may not be caused in full by diabetes. If for example diabetes is stated as secondary diagnosis for a patient discharged from hospital because of a malignant disease, at most a minority of the costs may be attributable to diabetes.

Costs of hypoglycaemic agents stems from the national prescription database and contain all prescriptions redeemed in pharmacies. Costs related to drugs provided in hospitals are included in the DRG reimbursement to hospitals. Pharmaceuticals used to prevent or treat diabetes related complications are difficult to quantify, but lipid lowering and antihypertensives are included on the basis of the patient survey.

The NLWA keeps account of reimbursement for diabetes related medical devices and these costs are likely to be complete. Also, drug costs are quite accurate because all pharmacies register prescriptions electronically and transfer their data to the central registry.

Table 9 Basic and supplemental benefits related to diabetes*

	Number of patients	Expenditure (million €)
Basic benefits	1058	1.4
Supplemental benefits	1876	3.9
Total	2934	5.3

* Approximately 15% of overall receivers of basic and supplemental benefits are lacking diagnosis in the database

We have included some types of costs that we consider relevant for persons with diabetes, such as doctor home visits related to hypoglycaemia, nutritionist guidance, foot therapy, physiotherapy and acupuncture. We can not attribute all costs gathered in the patient survey to diabetes. For example, there are reasons other than diabetes for having acupuncture. It should be noted that the survey we undertook may not be entirely representative of the diabetes population in Norway, especially for type 2 diabetes. Some cost estimates (GP home visits for hypoglycaemia, foot therapy, nutritional guidance, physiotherapy, acupuncture, costs of cholesterol lowering- and antihypertensive drugs) may consequently be biased, but the impact on any bias will be small because the relevant costs were small.

Our study provides some important general lessons about the cost structure of diabetes care. First, the main direct cost-drivers from diabetes are hospital services, pharmaceuticals and medical devices. These services are reimbursed in part or in full by governments in most industrialised countries. Second, other types of services such as foot therapy, physiotherapy, and acupuncture may represent considerable costs, but often receive only partial and sometimes no reimbursement by governments. In Norway, the use of foot therapy is paid in full by the patient, while in contrast the cost of foot ulcer treatment and amputations is covered almost fully by the government. This may seem paradoxical as untreated foot ulcers may lead to infections and ultimately amputation. Finally, the study reveals a high level of spending on acupuncture compared to much lower spending on nutritional guidance. Given the importance of diet for the progress of the disease, this result is somewhat paradoxical and suggests that patients could benefit from a different spending pattern.

We found that hospital costs with diabetes as main diagnosis were twice as high for type 1 diabetes as for type 2. However, a large proportion of those with non-insulin-dependent diabetes had CVD as the primary diagnosis. Diabetes is likely an important causal factor for CVD among these patients which indicates that type 2 diabetes still is a major cost driver. It is therefore likely that type 2 diabetes is more important than type 1 diabetes with respect to hospital costs.

The number of individuals on oral glucose lowering drugs was almost twice the number of users of insulin and analogues. In terms of costs, the pattern was opposite in that the total cost of insulin and analogues was twice the cost of oral glucose lowering drugs. This indicates that treatment of type 2 diabetes becomes more

costly with disease progression because insulin is increasingly prescribed with progression.

Our results are somewhat different from those reported elsewhere. In Sweden the estimated costs of hypoglycaemia related to type 2 diabetes was €14.10 per patient per year [20] while our data would suggest about €3 per patient. The Swedish costs are higher because of a higher reported prevalence of hypoglycaemia and the inclusion of indirect costs.

One should be aware of methodological differences when comparing the results of cost-of-illness analyses. We used a prevalence approach; studies relying on an incidence approach with prediction of future costs may yield higher values. Also, the method for valuing absence from productive work may have considerable impact on the results of cost-of-diabetes studies. Clearly, the more types of diabetes related costs that are included, the higher the estimated costs. A recent review [21] suggests that there is a general tendency for indirect costs to make up a slightly larger proportion of total costs than direct costs. In the studies reviewed, the proportion of indirect costs was in the range of 25-64%.

A study performed in Ireland [22] estimated that the costs of treating diagnosed type 2 diabetes was 4.1% of the total health care expenditure. Hospitalisations accounted for almost half of overall costs, while ambulatory and medicines costs accounted for 27% and 25%.

In an early Swedish [3] study, the costs of diabetes amounted to 5.7 billion Swedish Kroner (SEK) (€570 million) of which 43% represented direct costs. Hospital care estimates were based on the main diagnosis and represented the main component of direct costs. The distribution among the different types of direct costs were about the same in the Swedish study as our. The indirect costs in the Swedish study represented 57% of the total compared to 24% in our study when including only hospital admissions with diabetes as the main diagnosis. This difference is in part attributable to the fact the Swedish study included productivity losses caused by premature mortality while ours did not. Whether the remaining difference between the two studies is attributable to difference in time or difference in real costs is unclear.

In a recent Swedish study [23] which report increasing costs of diabetes over time, another approach to COI analysis is used. Diabetes prevalence and attributable risks for diabetes complications were used to estimate the diabetes-related costs. This approach should result in an estimate of the COI that is between estimates based on diabetes as the primary diagnosis and estimates based on diabetes as the primary as well as the secondary diagnosis.

The wide variation in methodology makes comparison of the results difficult and calls for standardisation of methods. Patient organisations might play a role in developing guidelines for COI studies. Additionally, there is a need for more research into how choice of methods impact the results using data from the same country and the same time rather than comparing across countries. Even though COI represent a basis for allocating research resources, most research should be directed at studies of intervention effectiveness and how care can be provided in the most efficient way. The latter in practice means cost-effectiveness studies, and our COI study could be used as a toolbox for analysts in need of cost data. If later studies are performed in the same way, it may provide useful insight in how costs develop over time.

Conclusions

In conclusion, the cost of diabetes represents 1.4% - 2.6% of the total health care expenditures in Norway, depending on how diabetes related hospitalisation is accounted for. The high diabetes costs indicate that society may do well in devoting resources to diabetes prevention and research.

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Authors' contributions

OS (lead author) developed the study design, collected data, performed the analyses, drafted the manuscript and approved the final version. TJ provided inputs on design, revised the manuscript during the writing and approved the final version. ISK provided inputs on design, revised the manuscript during the writing and approved the final version.

Competing interests

Trond Jenssen and Ivar Sønbø Kristiansen have received honoraria from various pharmaceutical companies that market drugs that may be used by persons with diabetes. Trond Jenssen is medical advisor to the Norwegian Diabetes Association.

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HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Health-related quality of life in diabetes: The associations of complications with EQ-5D scores

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Abstract

Background: The aim of this study was to describe how diabetes complications influence the health-related quality of life of individuals with diabetes using the individual EQ-5D dimensions and the EQ-5D index.

Methods: We mailed a questionnaire to 1,000 individuals with diabetes type 1 and 2 in Norway. The questionnaire had questions about socio-demographic characteristics, use of health care, diabetes complications and finally the EQ-5D descriptive system. Logistic regressions were used to explore determinants of responses in the EQ-5D dimensions, and robust linear regression was used to explore determinants of the EQ-5D index.

Results: In multivariate analyses the strongest determinants of reduced MOBILITY were neuropathy and ischemic heart disease. In the ANXIETY/DEPRESSION dimension of the EQ-5D, "fear of hypoglycaemia" was a strong determinant. For those without complications, the EQ-5D index was 0.90 (type 1 diabetes) and 0.85 (type 2 diabetes). For those with complications, the EQ-5D index was 0.68 (type 1 diabetes) and 0.73 (type 2 diabetes). In the linear regression the factors with the greatest negative impact on the EQ-5D index were ischemic heart disease (type 1 diabetes), stroke (both diabetes types), neuropathy (both diabetes types), and fear of hypoglycaemia (type 2 diabetes).

Conclusions: The EQ-5D dimensions and the EQ-5D seem capable of capturing the consequences of diabetes-related complications, and such complications may have substantial impact on several dimensions of health-related quality of life (HRQoL). The strongest determinants of reduced HRQoL in people with diabetes were ischemic heart disease, stroke and neuropathy.

Background

Diabetes is a chronic disease with serious short-term and long-term consequences for the afflicted. The total number of individuals with diabetes worldwide is projected to rise from about 170 million in 2000 to about 370 million in 2030 [1]. In the long term, diabetes causes microvascular complications (e.g. retinopathy and neuropathy) and macrovascular complications (e.g. myocardial infarction, angina pectoris and stroke). In addition to diabetes-related complications, episodes of hypoglycaemia, fear of hypoglycaemia, change in life style and fear of long term consequences may lead to reduced health-related quality of life (HRQoL). In fact, individuals with diabetes have reduced HRQoL compared with those without diabetes in the same age group [2,3], and their HRQoL decreases with disease progression and complications [4,5].

There are three main approaches to describe and measure HRQoL: Disease-specific instruments, generic instruments and utility instruments. Numerous disease-specific HRQoL measures exist for diabetes, and these score HRQoL on ordinal scales [6-8]. Generic instruments such as the Short Form 36 (SF-36) are also used [9]. In multi-attribute utility instruments (MAU), such as the EQ-5D [10], 15D [11], Health Utility index (HUI) [12,13] and SF-6D [14], respondents indicate levels of health problems on a number of dimensions of health. These values are translated into a zero-one scale where zero denotes death and one perfect health. Some utility instruments allow for negative values, meaning that some health states are considered worse than death. Preference-based methods such as the time trade-off method (TTO) [15], standard gamble (SG) or the visual analogue scale (VAS) may be used to develop translation algorithms. When the HRQoL weight

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is multiplied with duration (years, months, duration of effect, expected remaining life years) the product is denoted QALY (quality-adjusted life years) [16]. QALYs can be calculated for different patient groups to compare for example effectiveness of treatment, enabling health improvements and life extensions to be captured in one single variable.

EQ-5D [10] is a MAU instrument with five dimensions (MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN/DISCOMFORT and ANXIETY/DEPRESSION) and three levels on each dimension, and has previously been used in populations with diabetes [17]. EQ-5D has been used extensively in economic evaluation, and is recommended for use in cost-effectiveness analyses by institutions such as the National Institute for Clinical Excellence (NICE) in the UK and the Health Care Insurance Board in the Netherlands. Therefore, researchers working with economic evaluation, government agencies and the pharmaceutical industry need easy access to utility data for different types of patients.

Against this background the aim of this study was three-fold:

- To use the five individual EQ-5D dimensions to describe some aspects of HRQoL in a group of people with diabetes.
- To investigate the impact of self-reported diabetes-related complications on the EQ-5D dimension scores.
- To investigate determinants of EQ-5D index in order to offer researchers utility data for individuals with diabetes.

Methods

The data in this study stem from a Norwegian survey of people with diabetes in 2006. A questionnaire was developed and piloted among health care professionals, including physicians with diabetes expertise and the county leaders of the Norwegian Diabetes Association (NDA). The latter group served as representatives of the target group. The study was approved by the Regional Ethics Committee and the Norwegian Data Inspectorate.

The seven-page questionnaire captured background variables such as age, gender, location, income in Norwegian Kroner (NOK), smoking habits, height, weight, as well as diabetes-specific variables such as diabetes-related health complications and use of health services. Finally, respondents were presented with eight diabetes-specific HRQoL questions and an approved Norwegian translation of the EQ-5D descriptive system. EQ-5D responses were translated into EQ-5D index utilities using the UK TTO tariff [18].

The questionnaire was mailed to a sample of members of the Norwegian Diabetes Association. A large proportion of the individuals with type 1 diabetes in Norway are members of the NDA, while only a minority of those with type 2 diabetes are members. After excluding individuals under the age of 18 years and those without diabetes, such as health care workers and others with an interest in diabetes, the NDA drew a random sample of 1,000 members. Non-respondents were followed up twice. The last follow up was accompanied by a letter from the NDA explaining the importance of insight in diabetes and encouraging response.

Data analyses

For descriptive statistics, we used means, proportions and standard deviations. Determinants of EQ-5D dimension values were analysed by logistic regression. For all 5 dimensions level 2 and 3 on the EQ-5D dimensions were merged and thus dichotomized to "no problem" or "some or extreme problem". We performed separate regressions for type 1 and type 2 diabetes.

The EQ-5D index was analysed with a linear OLS regression model. The Breusch-Pagan test and plotting residuals versus fitted values showed that heteroscedasticity was present both for type 1 and type 2 diabetes. Therefore, we applied White's robust variance estimators.

The data were complete except for the covariates "Fear of hypoglycaemia" (13% missing), "Limitations at work" (23% missing) and "Limitations socially" (10% missing). Missing values were therefore imputed with regressions based on 15 independent variables (sex, age, weight, height and 11 diabetes-related complications). We used the impute function in STATA, which runs regressions by simple best-subset linear regression, looking at the pattern of missing values in the predictors.

We tested the covariates age and body mass index first as dummy variables divided in quartiles and second as continuous variables.

We chose covariates for the models based on input from health care professionals and representatives from academia. In the binary regressions the selected variables are considered plausible to be linked with the dimension analysed. In addition to "Sex" and "age", all direct medical complications were included in all dimensions except "Proteinuria". We believe this covariate is likely only to remind the individuals of lurking complications and should thus only impact the ANXIETY/DEPRESSION dimension. The variable "Impaired vision" is in our view not likely to directly cause pain or discomfort and is not included in regression of the PAIN/DISCOMFORT dimension. Emotional impact of impaired vision should be captured in the ANXIETY/DEPRESSION dimension.

In both the logistic binary and the linear regressions full sets of the selected covariates were kept throughout

the analysis in order to provide variables with both significant and non-significant impact on the covariates. For the linear regression this would provide a full set of results which may be used by other analysts in decision analytic modelling.

All analyses were performed in STATA/SE 10.0 (Stata Corp, College Station, TX, USA).

Results

Sample characteristics

Of the total 1,000 eligible individuals with diabetes, 17 were excluded because they had died (n = 4) or had unknown address (n = 13). Two persons declined to participate. In total 598 of those eligible returned the questionnaire, of which 521 were complete and could be used in further analysis (response rate 53%). Among non-respondents, 51% were female compared with 47% among respondents.

Among the 521 respondents, 165 reported having type 1 diabetes (53% female), and 356 type 2 diabetes (44% female) (Table 1). Further descriptive statistics about demographics, risk, factors for complications, medication and complications are shown in Table 1.

Table 1 Characteristics of the respondents according to diabetes type, number (%), unless otherwise specified

	Type 1	Type 2
n	*165*	*356*
Demographics		
Sex, female	87 (53)	157 (44)
Age, mean (SD)	47.0 (14.9)	64.0 (11.7)
Annual family income (1000 NOK), mean (SD)	666 (908)	713 (3051)
Complication risk factors		
Diabetes duration (years), mean (SD)	22.1 (14.2)	10.0 (8.1)
Current smoking	47 (29)	62 (18)
Daily smoker	22 (14)	42 (12)
Occasional smoker	25 (15)	20 (6)
Previous smokers	86 (55)	200 (61)
Body mass index, kg/m^2 , mean (SD)	25.8 (4.8)	28.9 (5.1)
Medication		
Number of oral antidiabetic agents		
0	159 (96)	103 (29)
1	4 (2)	149 (42)
2	2 (1)	87 (24)
3	—	16 (5)
4	—	1 (0.3)
Insulin		
Short-acting insulin	152 (92)	68 (19)
Long-acting insulin	103 (62)	98 (28)
Insulin glargine (Lantus) or insulin detemir (Levemir)	51 (31)	11 (3)
Antihypertensives	52 (33)	217 (63)
Cholesterol lowering drug	45 (28)	205 (59)
Self-reported complications		
Impaired vision	31 (19)	51 (14)
Myocardial infarction	4 (2)	38 (11)
Angina	10 (6)	27 (8)
Reduced kidney function (Proteinuria)	15 (9)	24 (7)
Kidney transplant	1 (1)	2 (1)
Foot ulcer	6 (4)	13 (4)
Amputation	2 (1)	1 (0.3)
Stroke	5 (3)	19 (5)
Neuropathy	12 (7)	17 (5)
Other	37 (22)	53 (15)
None	79 (47)	161 (45)

Health-related quality of life

In total 10% of those with type 1 diabetes had problems with MOBILITY as judged from the EQ-5D, 3% with SELF-CARE, 19% with USUAL ACTIVITIES, 34% with PAIN/DISCOMFORT and 35% with ANXIETY/DEPRESSION (Table 2). For Type 2 diabetes the numbers were 26%, 6%, 25%, 45% and 33%, respectively. The mean EQ-5D index score was 0.83 (SD 0.24) in type 1 diabetes and 0.81 (SD 0.22) in type 2 (p = 0.32). The proportion of type 2 diabetes patients with fear of hypoglycaemia was 50% among those on insulin and 26% among the others.

For individuals without any reported complications, the mean EQ-5D index scores were 0.90 for those with type 1 diabetes and 0.85 for those with type 2 (Table 3). The presence of one complication decreased values to 0.76 and 0.80, respectively. With two or more diabetes-related complications the values were 0.55 and 0.64, respectively.

Regression analyses

In the binary logistic regressions of type 1 diabetes on EQ-5D dimension responses (Table 4), ischemic heart disease, foot ulcer, neuropathy, body mass index and receiving help from others were statistically significant determinants for reporting problems in the MOBILITY dimension. None of the covariates had impact on the SELF-CARE dimension. Disability pension and limitations at work had an impact on the USUAL ACTIVITIES dimension. Age, ischemic heart disease and neuropathy had an impact on the PAIN/DISCOMFORT dimension, and age, impaired vision, ischemic heart disease, neuropathy and fear of hypoglycaemia had an impact on the ANXIETY/DEPRESSION dimension.

For type 2 diabetes (Table 5), age, impaired vision, stroke, neuropathy, body mass index and receiving help from others were statistically significant determinants of MOBILITY. Receiving help from others for SELF-CARE, sex, stroke, disability pension, receiving help from others

Table 2 Distribution of levels of perceived problem in each of the dimensions of the EQ-5D descriptive system, according to diabetes type

	Type 1 (n = 165)			Type 2 (n = 356)		
	Level of perceived problem, %					
Dimension	1*	2*	3*	1*	2*	3*
Mobility	90	10	0	74	26	0
Self-care	97	3	0	94	6	0
Usual activities	81	18	1	74	24	1
Pain/discomfort	65	29	5	56	41	4
Anxiety/depression	65	32	3	67	30	3

* Level 1 implies no problem, 2 moderate problem, 3 severe problem

and limitations at work were associated with USUAL ACTIVITIES. Ischemic heart disease, neuropathy and hypoglycaemia had an impact on PAIN/DISCOMFORT. Age, foot ulcers, number of hospital admissions during the previous 6 months and fear of hypoglycaemia were associated with ANXIETY/DEPRESSION scores.

In the linear regression of the EQ-5D index for type 1 diabetes, presence of ischemic heart disease had a negative impact (-0.181), along with stroke (-0.291), neuropathy (-0.358), receiving disability pension (-0.111) and social limitations (-0.107) (Table 6). For type 2 diabetes the following conditions had a negative impact (Table 6): stroke (-0.135), neuropathy (-0.187), disability pension (-0.100), receiving help from others (-0.123), fear of hypoglycaemia (-0.078) and limitations at work (-0.087). For both diabetes types we tested for interactions, but found none. We found no effect of age or body mass index in the linear regressions whether age and BMI were entered as one continuous variable or as dummy variables.

Discussion

In this study, individuals with diabetes-related complications had reduced HRQoL, though the impact on HRQoL was somewhat different for type 1 and type 2 diabetes. Stroke and neuropathy had a negative impact on overall HRQoL in both types of diabetes, while ischemic heart disease and social limitations had an impact on those with type 1 diabetes, and fear of hypoglycaemia and limitations at work had an impact on those with type 2 diabetics. Individuals with type 1 diabetes reported more problems than those with type 2 in the PAIN/DISCOMFORT and ANXIETY/DEPRESSION dimensions, while in the MOBILITY, SELF-CARE and USUAL ACTIVITIES dimensions it was opposite. In spite of the limited descriptive system of the EQ-5D, the instrument still captures the impact of several diabetes complications both with respect to each of the dimensions and the EQ-5D index, and therefore individual EQ-5D dimensions seem well suited to capture most diabetes-related complications.

In a 2009 review of quality of life measurement in adults with diabetes [19] the authors claim that the EQ-5D measures quality of health and not quality of life and that the EQ-5D lacks responsiveness for use in diabetes. The authors state that while the EQ-5D may capture differences due to diabetes related complications it will not necessarily be able to capture differences across treatment regimens. This is because the extent to which a given treatment is considered flexible or convenient will not affect quality of health but may affect aspects of quality of life, such as social or working life. The authors suggest using diabetes-specific instruments or a different generic instrument more sensitive to differences between treatments. Our results show that while both the individual dimensions of the EQ-5D and the EQ-5D index are able to capture typical diabetes-related complications, the subgroups without complications reported surprisingly high EQ-5D index values. This may indicate that the EQ-5D instrument was not able to capture important non-health aspects of quality of life, as claimed in the review [19]. Because the EQ-5D instrument is not diabetes specific, lowered scores may reflect the impact of unrelated comorbidity. A condition specific instrument such as the ADDQoL may differentiate better between diabetes related complications and unrelated comorbidity [19].

In the present study, the finding that individuals with type 1 diabetes reported better HRQoL than those with type 2 can be explained by the younger age of the former group. The opposite was observed in subgroups with complications, and it seems as if diabetic complications had more impact on HRQoL in type 1 diabetes than type 2. A possible explanation is that complications

Table 3 Mean EQ-5D index utility values with and without diabetes-related complications

	Type 1 diabetes			Type 2 diabetes		
Number of complications	EQ-5D index	95% CI	n	EQ-5D index	95% CI	n
0	0.90	0.88 - 0.93	111	0.85	0.82 - 0.87	241
1	0.76	0.66 - 0.86	35	0.80	0.75 - 0.85	68
≥ 2	0.55	0.37 - 0.73	19	0.64	0.56 - 0.71	47
Any complication	0.68	0.59 - 0.77	54	0.73	0.69 - 0.78	115
All patients	0.83	0.79 - 0.87	165	0.81	0.79 - 0.83	356

Table 4 Binary multivariate logistic regression of responses to the EQ-5D items in type 1 diabetics, odds ratios (95% CI)

	EQ-5D dimensions				
	Mobility	**Self-care**	**Usual activities**	**Pain/discomfort**	**Anxiety/ depression**
Sex (male = 0, female = 1)	0.63 (0.14 - 2.74)	0.25 (0.01 - 5.15)	0.67 (0.22 - 2.03)	0.45 (0.20 - 1.03)	1.12 (0.50 - 2.51)
Age (in 10 years)	1.33 (0.78 - 2.25)	1.37 (0.55 - 3.43)	0.93 (0.61 - 1.40)	1.36 (1.04 - 1.77)*	0.72 (0.55 - 0.94)*
Impaired vision (no = 0, yes = 1)	3.00 (0.53 - 16.85)	12.11 (0.49 - 297.88)	0.28 (0.07 - 1.15)	———	4.60 (1.57 - 13.46) **
Ischemic heart disease (no = 0, yes = 1)	11.72 (2.02 - 68.09)**	1.24 (0.05 - 31.42)	4.15 (0.73 - 23.64)	5.84 (1.29 - 26.40)*	6.82 (1.34 - 34.75) *
Proteinuria (no = 0, yes = 1)	———	———	———	———	0.47 (0.09 - 2.47)
Foot Ulcer (no = 0, yes = 1)	13.33 (1.33 - 133.29)*	6.20 (0.17 - 221.73)	10.04 (0.80 - 126.22)	3.24 (0.47 - 22.43)	1.06 (0.16 - 6.96)
Stroke (no = 0, yes = 1)	0.47 (0.02 - 8.99)	17.37 (0.49 - 610.92)	1.24 (0.09 - 16.83)	10.66 (0.75 - 152.16)	1.14 (0.13 - 10.21)
Neuropathy (no = 0, yes = 1)	7.17 (1.22 - 42.03) *	5.86 (0.41 - 83.43)	6.96 (1.45 - 33.44)	27.13 (3.13 - 235.07)**	4.61 (1.05 - 20.21) *
Body mass index (kg/m^2)	1.15 (1.02 - 1.30)*	———	———	———	———
Disability pension (no = 0, yes = 1)	———	———	4.64 (1.33 - 16.18)*	———	———
Number of hospital admissions during previous 6 months	———	———	———	———	1.22 (0.58 - 2.53)
Receives help from others (no = 0, yes = 1)	10.04 (2.03 - 49.69)**	10.28 (0.61 - 173.34)	1.90 (0.50 - 7.22)	———	———
Hypoglycaemia index#	———	———	———	1.59 (0.87 - 2.89)	1.29 (0.71 - 2.33)
Fear of hypoglycaemia## (small = 0, large = 1)	———	———	———	———	3.98 (1.78 - 8.93) **
Limitations at work## (small = 0, large = 1)	———	———	13.20 (3.38 - 51.53)***	———	———
Limitations socially## (small = 0, large = 1)	———	———	1.87 (0.65 - 5.37)	———	———
Log likelihood	-28.08	-9.96	-51.46	-85.06	-85.30

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Cells with dotted line indicate that the variable was not included in the model.

Self reported episodes of hypoglycaemia, with 4 levels of severity (level 1 = hypoglycaemia cured with the intake of for example fluids containing sugar, no help from other required, level 2 = hypoglycaemia cured with the intake of for example fluids containing sugar, help from others required, level 3 = hypoglycaemia with help from doctor required (no hospital admission), level 4 = hypoglycaemia resulting in hospital admission), then added with severity weights (level 1 × 1, level 2 × 2, level 3 × 3, level 4 × 4) and finally divided in 3 groups 0, 1-11 and 12 to max

Self reported on a scale from 1 to 5 (1 = not at all, 5 = very much), recoded to 2 levels (> and < than 2.5 due to imputed values having values with decimals)

are likely to have a greater impact on the health of people with type 1 diabetes precisely because they are younger, i.e. have less comorbidity and have not adjusted to the idea of accepting lesser health. The differences could also be explained by the fact that this younger subgroup has responsibilities such as work and family as well as relationship issues that are not found in the older subgroup with type 2 diabetes.

In the UKPDS 37 study [20] individuals with type 2 diabetes and no complications had a mean EQ-5D index value of 0.83, compared with 0.85 in our study. In type 2 diabetes with complications, our observed EQ-5D index value (0.73) was equal to that of the UKPDS 37 study. Taking into account that patient characteristics were similar in the UKPDS and our study, UK diabetes studies may be transferable to the Norwegian setting. In the UKPDS 37 study the EQ-5D detected significant differences between people with and without macrovascular complications, but not microvascular complications or using different treatment regimens. In our study the microvascular complication neuropathy had impact on the individual EQ-5D dimensions and on the EQ-5D index.

In another UK study [21] of individuals with type 2 diabetes, the change in utility associated with fear of hypoglycaemia was relatively small compared with the disutility for serious diabetic complications such as neuropathy. Similarly, in our study fear of hypoglycaemia caused a reduction in utility of 0.021 (type 1 diabetes) and 0.078 (type 2), while the disutility of neuropathy was larger with 0.358 (type 1 diabetes) and 0.187 (type 2 diabetes). We have no clear explanation why our results indicate a lower impact on HRQoL of fear of hypoglycaemia in individuals with type 1 diabetes than those with type 2 diabetes. Fear of hypoglycaemia may not affect HRQoL particularly (e.g. has little impact on pain

Table 5 Binary multivariate logistic regression of responses to the EQ-5D items in type 2 diabetics, odds ratios (95% CI)

	EQ-5D dimensions				
	Mobility	**Self-care**	**Usual activities**	**Pain/ discomfort**	**Anxiety/ depression**
Sex (male = 0, female = 1)	0.68 (0.38 - 1.21)	0.59 (0.23 - 1.54)	0.47 (0.25 - 0.88)*	0.82 (0.53 - 1.27)	0.91 (0.54 - 1.52)
Age (in 10 years)	1.36 (1.03 - 1.80)*	0.83 (0.55 - 1.25)	1.34 (1.00 - 1.80)	1.03 (0.83 - 1.24)	0.78 (0.62 - 0.99)*
Impaired vision (normal = 0, reduced = 1)	2.96 (1.44 - 6.10)**	2.29 (0.77 - 6.75)	0.89 (0.39 - 2.04)	———	1.46 (0.71 - 3.01)
Ischemic heart disease (no = 0, yes = 1)	1.97 (0.91 - 4.25)	1.77 (0.54 - 5.86)	1.14 (0.48 - 2.71)	2.51 (1.27 - 4.97)**	1.15 (0.53 - 2.50)
Proteinuria (no = 0, yes = 1)	———	———	———	———	0.42 (0.14 - 1.29)
Foot Ulcer (no = 0, yes = 1)	0.32 (0.07 - 1.39)	0.73 (0.11 - 4.67)	2.11 (0.48 - 9.39)	2.18 (0.54 - 8.79)	7.00 (1.53 - 31.97)*
Stroke (no = 0, yes = 1)	3.50 (1.13 - 10.82)*	1.45 (0.23 - 9.13)	4.48 (1.38 - 14.59)*	1.99 (0.72 - 5.54)	2.14 (0.69 - 6.62)
Neuropathy (no = 0, yes = 1)	12.07 (3.30 - 44.12)***	2.74 (0.57 - 13.25)	3.08 (0.84 - 11.26)	Predicts perfectly#	1.29 (0.40 - 4.16)
Body mass index (kg/m^2)	1.12 (1.05 - 1.19)***	———	———	———	———
Disability pension (no = 0, yes = 1)	———	———	2.38 (1.20 - 4.69)*		———
Number of hospital admissions during previous 6 months	———	———	———	———	1.87 (1.14 - 3.07)*
Receives help from others (no = 0, yes = 1)	5.85 (3.00 - 11.38)***	6.95 (2.58 - 18.73)***	4.67 (2.21 - 9.87)***	———	———
Hypoglycaemia index##	———	———	———	1.68 (1.13 - 2.49)*	1.08 (0.70 - 1.68)
Fear of hypoglycaemia### (small = 0, large = 1)	———	———	———	———	5.76 (3.36 - 9.87)***
Limitations at work### (small = 0, large = 1)	———	——	6.95 (3.56 -13.56)***	———	———
Limitations socially### (small = 0, large = 1)	———	——	1.33 (0.67 - 2.62)	———	———
Log likelihood	-156.08	-66.13	-136.85	-232.10	-187.32

* p < 0.05, **p < 0.01, ***p < 0.001

All patients reporting neuropathy also reports having problems in the PAIN/DISCOMFORT dimension of the EQ-5D.

Cells with dotted line indicate that the variable was not included in the model.

Self reported episodes of hypoglycaemia, with 4 levels of severity (level 1 = hypoglycaemia cured with the intake of for example fluids containing sugar, no help from other required, level 2 = hypoglycaemia cured with the intake of for example fluids containing sugar, help from others required, level 3 = hypoglycaemia with help from doctor required (no hospital admission), level 4 = hypoglycaemia resulting in hospital admission), then added with severity weights (level 1 × 1, level 2 × 2, level 3 × 3, level 4 × 4) and finally divided in 3 groups 0, 1-11 and 12 to max

Self reported on a scale from 1 to 5 (1 = not at all, 5 = very much), recoded to 2 levels (> and < than 2.5 due to imputed values having values with decimals)

or mobility) but it can affect aspects of more general quality of life (e.g. independence, spontaneity, ability to work, enjoyment of leisure activities).

In a US review [22] of body weight and HRQoL in type 2 diabetes, the authors found decreasing HRQoL with increasing body weight in all included studies. When adjusting for other explanatory variables, we observed no significant impact of BMI on HRQoL.

A subgroup of individuals with unspecified type diabetes (n = 117) in a Swedish general population EQ-5D study [23], also using the UK tariff, reported a higher frequency of problems in all dimensions of the EQ-5D, than in both diabetes categories in our study. Further, the respondents in the study reported a lower mean EQ-5D index (0.74) than we observed in both type 1 and type 2 diabetes.

Some limitations of the present study should be noted. The respondents in the survey may not be representative of the population with diabetes. In particular, bias may arise because sicker and older persons with type 2 diabetes did not respond to the survey. A large proportion of individuals with type 1 diabetes in Norway (about 20,000) are members of the NDA while only a smaller proportion of the type 2 (about 100,000) are members of this organization. Clearly, our study does not capture HRQoL in undiagnosed diabetes patients. In

Table 6 Linear multivariate regression of EQ-5D index, according to diabetes type

	Type 1		Type 2	
N	165		356	
	Coefficient (95% CI)	P > |t|	Coefficient (95% CI)	P > |t|
Constant	1.092 (0.921 to 1.263)	<0.001	0.990 (0.787 to 1.193)	<0.001
Sex (male = 0, female = 1)	0.041 (-0.023 to 0.105)	0.210	0.024 (-0.016 to 0.064)	0.240
Age (in 10 years)	-0.003 (-0.022 to 0.016)	0.749	0.0004 (-0.017 to 0.017)	0.967
Impaired vision (no = 0, yes = 1)	-0.063 (-0.169 to 0.044)	0.245	-0.012 (-0.074 to 0.051)	0.711
Ischemic heart disease (no = 0, yes = 1)	-0.181 (-0.331 to -0.031)	0.019	-0.037 (-0.103 to 0.030)	0.276
Proteinuria (no = 0, yes = 1)	0.089 (-0.036 to 0.215)	0.161	0.043 (-0.019 to 0.106)	0.174
Foot Ulcer (no = 0, yes = 1)	-0.083 (-0.271 to 0.105)	0.383	-0.016 (-0.134 to 0.101)	0.783
Stroke (no = 0, yes = 1)	-0.291 (-0.475 to -0.108)	0.002	-0.135 (-0.247 to -0.023)	0.018
Neuropathy (no = 0, yes = 1)	-0.358 (-0.535 to -0.180)	<0.001	-0.187 (-0.316 to -0.057)	0.005
Body mass index (kg/m^2)	-0.004 (-0.008 to 0.001)	0.123	-0.002 (-0.007 to 0.002)	0.307
Disability pension (no = 0, yes = 1)	-0.111 (-0.191 to -0.030)	0.008	-0.100 (-0.153 to -0.046)	<0.001
Number of hospital admissions during previous 6 months	0.003 (-0.042 to 0.049)	0.880	-0.028 (-0.076 to 0.020)	0.255
Receives help from others (no = 0, yes = 1)	-0.090 (-0.217 to 0.037)	0.166	-0.123 (-0.185 to -0.060)	<0.001
Hypoglycaemia index#	-0.023 (-0.071 to 0.025)	0.337	-0.004 (-0.039 to 0.032)	0.839
Fear of hypoglycaemia## (small = 0, large = 1)	-0.021 (-0.073 to 0.031)	0.432	-0.078 (-0.129 to -0.028)	0.003
Limitations at work## (small = 0, large = 1)	-0.023 (-0.089 to 0.043)	0.494	-0.087 (-0.148 to -0.025)	0.006
Limitations socially## (small = 0, large = 1)	-0.107 (-0.188 to -0.026)	0.010	-0.002 (-0.049 to 0.046)	0.944

Self reported episodes of hypoglycaemia, with 4 levels of severity (level 1 = hypoglycaemia cured with the intake of for example fluids containing sugar, no help from other required, level 2 = hypoglycaemia cured with the intake of for example fluids containing sugar, help from others required, level 3 = hypoglycaemia with help from doctor required (no hospital admission), level 4 = hypoglycaemia resulting in hospital admission), then added with severity weights (level 1 × 1, level 2 × 2, level 3 × 3, level 4 × 4) and finally divided in 3 groups 0, 1-11 and 12 to max ## Self reported on a scale from 1 to 5 (1 = not at all, 5 = very much), recoded to 2 levels (> and < than 2.5 due to imputed values having values with decimals)

line with other patient surveys, we had 47% non-response. We have no information on non-respondents except for sex (based on non-respondents first names), and here there was little difference between responders and non-responders.

It is important to be aware that because the EQ-5D instrument is no diabetes specific it may reflect problems related to other conditions. Our study was performed at one point in time, and fluctuations are likely to occur if HRQoL was measured at multiple points in time. The observed associations are not necessarily causal. Further they are limited by the lack of serial observations. Furthermore, the limited sample size, especially for type 1 diabetes may limit the power for some of the comparisons of presence or absence of complications.

Note that despite the index score being a function of the score in the dimensions a significant impact on linear regression of the index does not necessarily imply a significant impact on one or more of the dimensions. This is the case for the covariate "stroke" which is significant in both types of diabetes in the linear regression by not significant in any of the dimensions in the type 1 diabetes group.

Lacking a Norwegian EQ-5D tariff we used the UK tariff, based on TTO [18]. This tariff is probably the most commonly used EQ-5D tariff globally, and quite similar to the Danish one [24]. Also, one small Norwegian study indicates that UK and Norwegian values are quite similar [25].

Conclusions

In this sample of people with diabetes, the individual EQ-5D dimensions were able to capture diabetes-related complications. The results show that such complications may have an impact on many dimensions of health-related quality of life, and the impact may be substantial. The strongest determinants of reduced HRQoL, as assessed with the EQ-5D index, were ischemic heart disease, stroke and neuropathy. The complexity of the disease means that several dimensions need to be considered when priorities are set for diabetes interventions.

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Authors' contributions
OS developed the study design, collected data, performed the analyses and drafted the manuscript. KS and ISK provided inputs on design and revised the manuscript during the writing. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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III

APPENDIX

Appendix 1

English translation of the questionnaire used in the survey (Paper I and II)

PART I: ABOUT YOURSELF

1. Sex
Female
Male

2. Age?

3. Weight? kgs

4. Height? cm

5. What is your highest level of completed education?
University/college…… Primary/secondary school… High school/A-levels…

6. Which county do you live in? ……

7. Do you smoke?
Daily
Once in a while
Never

8. Have you smoked on a daily basis before?
Yes
No **If yes, please state number of years** **Years**

9. What is the aggregate pre-tax household income?

PART II: ABOUT YOUR DIABETES

10. Which form of diabetes do you have? (please select an alternative)
Type 1…… Type 2……
Other…… Uncertain……..

13. What was your last HbA1c blood sugar reading?
…,…%

11. In what year were you diagnosed with diabetes? (please state year in digits)

12. Has your diabetes led to any health-related problems/complications/associated diseases? (several answers possible)
Inpaired vision……
Cardiac infarction…….
Reduced renal function *(protenuria)*……
Angina *(chest pain associated with physical exertion))*....
Diabetic foot……
Stroke……..
Amputation……

Renal transplantation……

Neuropathy *(damage to the nerves)*……..

Uncertain……

No……..

Other, (please state), ……..……

PART III: DRUGS/MEDICATION

14. Do you use any of the following drugs? (please check)

Tablets:

Actos …….

Glucobay ……..

Amaryl …….

Glipizid…….

Apamid……..

Metformin ……

Avandia.....

Minidiab ……

Avandamet ……

Novonorm …….

Glibenclamid…….

Starlix……

Glucophage……..

Insulin:

Lantus …….

Insulin (long acting)…….

Levemir …….

Insulin (short acting)…….

15. Du you use any antihypertensive drugs?

Yes

No

Uncertain

16. Du you use any cholesterol-lowering drugs

Yes

No

Not sure

17. Do you use any other medications on a regular basis? :

Yes

No

Not sure…… , ……

18. Have you experienced hypoglycemia in the course of the last 6 months?

Yes

No

If yes, please state the number of times according to the description of the severity

Transient hypoglycemia which goes away following the intake of e.g. a sugary drink without the assistance of next of kin/others…….times

Transient hypoglycemia which goes away following the intake of e.g. a sugary drink with the assistance of next of kin/others ……. times

Hypoglycemia requiring the attention of a doctor (without hospitalisation)……. times

Hypoglycemia with hospitalisation……. times

PART IV: DOCTOR AND HOSPITAL VISITS

19. We will now ask you about your consumption of other health services in the course of the last 6 months. Please state the number of visits:

General practitioner…… times
Nutritionist/dietician. times
Specialist in private practice times
Foot therapist…… times
Hospitalised…. times
Physiotherapist……..… times
Out-patient visits times
Acupuncture…… times

20. If you have been hospitalised in the course of the last 6 months: For how long were you admitted? (please state the appropriate number of days in the table below (on a maximum of 8 occasions)).

1st time…… days
2nd time…… days
3rd time……. days
4th time……. days
5th time…….. days
6th time…….. days
7th time…….. days
8th time…….. days

PART V: EQUIPMENT

21. We will now inquire about your consumption of medical equipment associated with your diabetes in the course of the last 6 months.

Do you use an insulin pump? Yes No

State the number of items used in the course of the last 6 months:

Infusion set (for insulin pump) .....

Home measurement of urine ketones (self-tester)……

Home measurement of blood sugar (self-tester).....

Home measurement of urine blood sugar (self-tester) ……

Insulin pens……

Lancets for blood sugar measurement…….

Insulin pen needles.....

PART VI: SICKNESS AND SOCIAL BENEFITS

22. For how many weeks have you been away on sick leave in the course of the last 6 months weeks

23. Do you receive disability benefit?
Yes
No

24. Was diabetes the reason for your disability benefit

Yes

No

Not sure

25. Disability benefit degree (please state percentage) %

26. Do you receive basic benefit (grunnstønad), assistance benefit (hjelpestønad) or augmented assistance benefit (forhøyet hjelpestønad) from the National Insurance Administration due to diabetes? (please check, several answers possible)

Basic benefit……

Augmented assistance benefit

Assistance benefit……...

No……

27. If you reached maximum co-payment level 1 and were entitled to an Exemption Card (frikort) during 2006, in which month was this?

Please enter the number of the month here:

Januar = 01
Februar = 02 osv.

28. If you reached maximum co-payment level 2 and were entitled to an Exemption Card (frikort) during 2006, in which month was this?

Please enter the number of the month here:

Januar = 01
Februar = 02 osv.

PART VII: YOU AND YOUR FAMILY

29. Does your diabetes make you dependent on your next of kin/family/close friends with regard to particular activities? (if yes, please check the relevant boxes in the table below, several answers possible)

Administer injections ……

Clean the house……..

Tablet dosing …...

Spend time outdoors……

Cook……

30. Has anyone in your family had to take time off work to assist or support you in the course of the last 6 months as a consequence of your diabetes?
Yes
No

31. If yes, please state the number of days: days

PART VIII: QUALITY OF LIFE

We will now ask you some questions pertaining to quality of life. The questions below are drawn from a standard questionnaire used to measure quality of life associated with various health conditions. We would like to ask you to select the answer which best represents/fits/describes your average condition over the last 6 months.

32. Does diabetes affect your daily life? (if yes, select the box corresponding to the extent, in the table. Several answers are possible 1 means "not at allt" while 5 is "to a great extent")

	1	2	3	4	5
I can't eat whatever I like……..	☐	☐	☐	☐	☐
I suffer from fatigue……	☐	☐	☐	☐	☐
I'm afraid of becoming hypoglycemic……	☐	☐	☐	☐	☐
I'm afraid of my blood sugar level becoming too high	☐	☐	☐	☐	☐
I'm afraid of complications that might arise because of my diabetes …	☐	☐	☐	☐	☐
Diabetes limits my choice and pursuit of a career ……..…	☐	☐	☐	☐	☐
Diabetes limits my leisure activities.……..	☐	☐	☐	☐	☐
Diabetes limits my participation in social activities and organisations…	☐	☐	☐	☐	☐

33. Mobility

I have no problem walking around……..	☐
I have some problems walking around……..	☐
I am bedridden…….	☐

34. Self care

I have no problems with regard to personal care……..	☐
I have some problems washing and/or dressing myself…..	☐
I am unable to wash and or dress myself……	☐

35. Usual activities (e.g. work, studies, household chores, and family or leisure activities).

I have no problems with regard to my regular activities……..	☐
I have some problems with regard to my regular activities…	☐
I am unable to take part in any regular activities……	☐

36. Pain and discomfort

I experience neither pain nor discomfort…….	☐
I experience moderate pain/discomfort……..	☐
I experience strong pain/discomfort ……	☐

37. Anxiety and depression

I am neither anxious nor depressed……..	☐
I am anxious/depressed to some degree……....	☐
I am very anxious/depressed……	☐

DO YOU HAVE ANY COMMENTS WITH REGARD TO OUR INVESTIGATION? IF SO, PLEASE STATE THEM HERE

_____
_____
_____
_____
_____

Thank you for taking the time to answer our numerous questions!

Please slip the questionnaire in the enclosed envelope and put it in the mail.

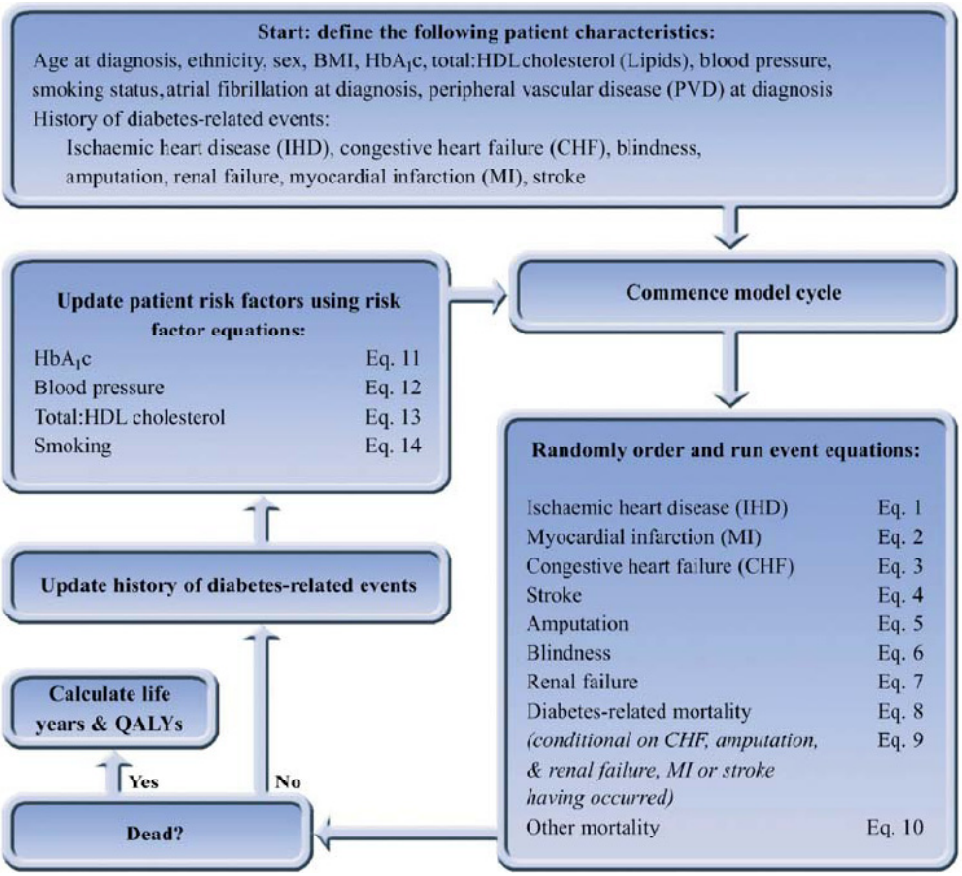
Appendix 2

The EQ-5D UK tariff value set

UK VAS VALUE SET		Example: THE VALUE SET FOR HEALTH STATE 21232	
Full health (11111)	1	Full health	1
At least one 2 or 3 (constant)	- 0.155	Minus constant	-0.155
At least on 3 (N3)	- 0.215	Minus N3	-0.215
Mobility = 2	- 0.071	Minus MO level 2	-0.071
Mobility = 3	- 0.182		
Self care = 2	- 0.093	Minus SC level 1	-0.000
Self care = 3	- 0.145		
Usual activities = 2	- 0.031	Minus UA level 2	-0.031
Usual activities = 3	- 0.081		
Pain/discomfort = 2	-0.084	Minus PD level 3	-0.171
Pain/discomfort = 3	-0.171		
Anxiety/depression = 2	-0.063	Minus AD level 2	-0.063
Anxiety/depression = 3	-0.124		
		STATE 21232	0.294

Appendix 3

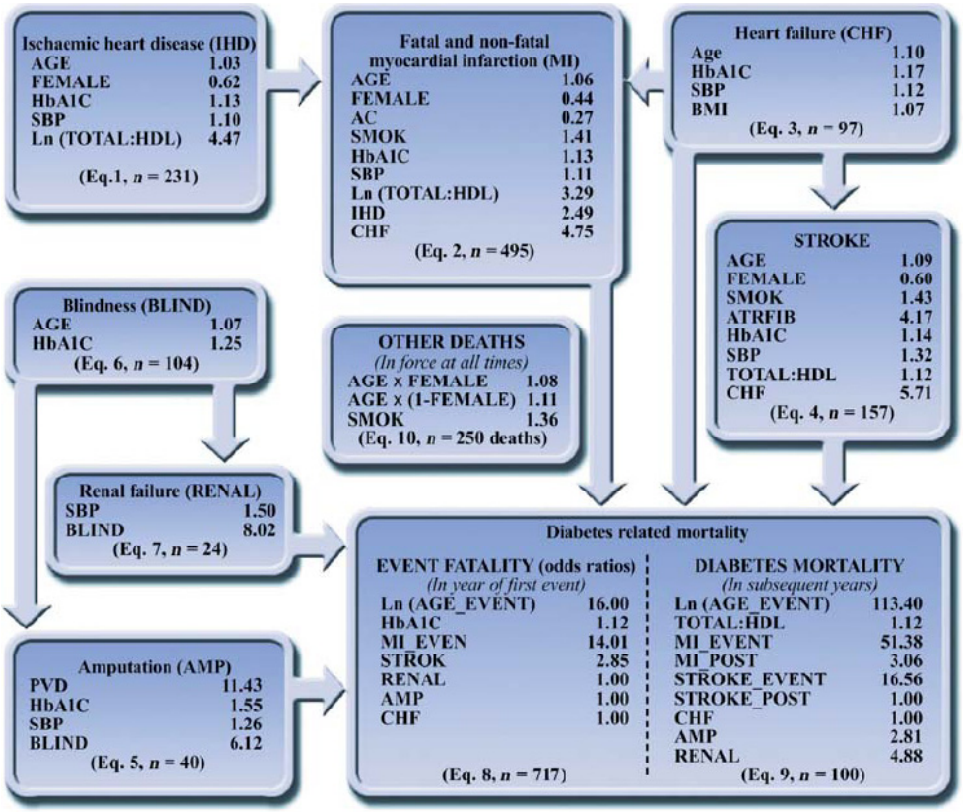
UKPDS Outcomes Model structure



Source: Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 October;47(10):1747-59.

Appendix 4

UKPDS Outcomes Model equations – overview



Source: Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 October;47(10):1747-59.

Appendix 5

The event equations of the UKPDS Outcomes Model

	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Eq. 5	Eq. 6	Eq. 7
Complication	IHD	MI	CHF	STROKE	AMP	BLIND	RENAL
No. of subjects	3612	3642	3607	3607	3642	3642	3642
Functional form	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
Parameters	Estimate of coefficient (SE)						
λ	−5.310 (0.174)	−4.977 (0.160)	−8.018 (0.408)	−7.163 (0.342)	−8.718 (0.613)	−6.464 (0.326)	−10.016 (0.939)
ρ	1.150 (0.067)	1.257 (0.060)	1.711 (0.158)	1.497 (0.126)	1.451 (0.232)	1.154 (0.121)	1.865 (0.387)
AGE	0.031 (0.008)	0.055 (0.006)	0.093 (0.016)	0.085 (0.014)		0.069 (0.014)	
FEMALE	−0.471 (0.143)	−0.826 (0.103)		−0.516 (0.171)			
AC		−1.312 (0.341)					
SMOK		0.346 (0.097)		0.355 (0.179)			
BMI			0.066 (0.017)				
HBA1C	0.125 (0.035)	0.118 (0.025)	0.157 (0.057)	0.128 (0.042)	0.435 (0.066)	0.221 (0.050)	
SBP	0.098 (0.037)	0.101 (0.026)	0.114 (0.056)	0.276 (0.042)	0.228 (0.075)		0.404 (0.106)
TOTAL:HDL				0.113 (0.025)			
Ln (TOTAL:HDL)	1.498 (0.202)	1.190 (0.169)					
PVD					2.436 (0.521)		
ATRFIB				1.428 (0.472)			
IHD		0.914 (0.150)					
CHF		1.558 (0.202)		1.742 (0.287)			
BLIND					1.812 (0.462)		2.082 (0.551)

Source: Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 October;47(10):1747-59.

Appendix 6

The mortality equations of the UKPDS Outcomes Model

	Eq. 8	Eq. 9	Eq. 10
Event	EVENT FATALITY	DIABETES MORTALITY	OTHER DEATH
No. of subjects	717	584	3642
Functional form	Logistic	Gompertz	Gompertz
Parameters	Estimate of coefficient (SE)		
λ	−3.251 (0.358)	−5.124 (0.363)	−6.373 (0.162)
φ		0.003 (0.038)	0.154 (0.016)
Ln (AGE_EVENT)	2.772 (0.716)	4.731 (1.066)	
AGE · (FEMALE)			0.081 (0.013)
AGE · (1-FEMALE)			0.104 (0.012)
SMOK			0.307 (0.141)
HBA1C	0.114 (0.053)		
TOTAL:HDL		0.109 (0.047)	
MI_EVENT	2.640 (0.336)	3.939 (0.275)	
MI_POST		1.119 (0.277)	
STROKE_EVENT	1.048 (0.376)	2.807 (0.408)	
RENAL		1.585 (0.315)	
AMP		1.032 (0.377)	

Source: Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 October;47(10):1747-59.

Appendix 7

The risk factor equations of the UKPDS Outcomes Model

	Eq. 11	Eq. 12	Eq. 13	Eq. 14
Risk factor	HBA1C	SBP	TOTAL:HDL	SMOK
No. of subjects	3631	3592	3520	3536
Type of regression	Panel	Panel	Panel	Logistic
$r2$	0.64	0.65	0.44	
Parameters	Estimate of coefficient (SE)			
α	−0.024 (0.017)	0.030 (0.014)	−0.021 (0.007)	−4.020 (0.236)
Ln (YEAR)	0.144 (0.009)	0.039 (0.008)		
YEAR				−0.203 (0.024)
YEAR_2	−0.333 (0.050)			
AGE				−0.027 (0.008)
FEMALE				−0.489 (0.154)
LHBA1C	0.759 (0.004)			
HBA1C_BASE	0.085 (0.004)			
LSBP		0.717 (0.004)		
SBP_BASE		0.127 (0.004)		
LTOTAL:HDL			0.526 (0.005)	
LTOTAL:HDL_BASE			0.252 (0.006)	
LSMOK				1.878 (0.211)
SMOK_BASE				4.879 (0.494)

Source: Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 October;47(10):1747-59.